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Use of Dose Calibrators in Medicine

Presented to Advisory Committee on the Medical Uses of Isotopes

September 20, 2012

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Why do we need dose calibrators?

Verify the amount of radioactivity patients are being administered.

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Why do we need to know the activity?

So we can estimate radiation absorbed doses to the organs and whole body.

Such doses not only depend on the (1) activity, but (2) patient size, and (3) biodistribution of the specific radiolabeled drug.

How organ dose coefficients and tables are generated is beyond the scope of this presentation.

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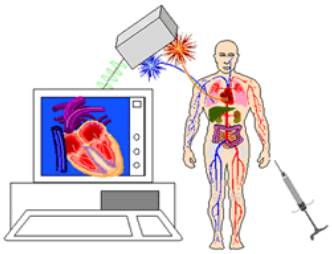
For a specific radiolabeled drug
Activity (Bq) → Radiation dose (Gy) to organs



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Accuracy of the dose is essential for therapy!

Deviations of ± 20% will impact on patient outcomes, consequently, in my opinion, external beam and brachytherapy radiation therapy are the most science based cancer treatments.

To ensure such precision and accuracy, radiation doses, equipment testing, and calibration are calculated with surprisingly consistent accuracy frequently, with qualified personnel!

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Calculating radiation dose from unsealed sources is more challenging.

- Knowledge of administered activity
- Patient specific biodistribution
- Patient size

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Precision and accuracy is becoming more important for diagnostic imaging.

- Accuracy is essential for imaging based standardized measurements, such as the calculation of standard uptake values (SUV), or monitoring cancer treatment.
- To monitor real changes in the patient, activity measurement variance must be less than the change in tumor size or metabolic activity.

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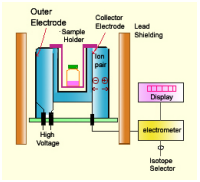
Dose Calibrators designed to verify clinically administered radioactivity are just one type of radiation detector

Dose Calibrator



Dose calibrators primarily for gamma emitters

Primarily measure ionization

Traceability to a reference standard, preferably the same radionuclide with same energies

Alternative detection technologies and protocols exist for validating the type and amount of radiation.

Calibration of particulate radiation more challenging

Microspheres (glass or resin encased Y-90) for hepatic cancer, or

Monoclonal antibodies for the CD-20 antigen in non-Hodgkins lymphoma

- Bexxar® , I-131 labeled tositumomab
- Zevalin® ,Y-90 labeled ibritumomab tiuxetan
- (Maximum dose is limited to 32.0 mCi,1.184 GBq of Y-90)

Precision and Accuracy of Radiolabeled Drugs is not comparable to External Beam Therapy

What is the radiation absorbed dose when we don't even know the tumor mass?

And why is "Maximum dose limited to 32.0 mCi (1.184 GBq) of Y-90 for Zevalin®"

Activity is limited for Patient Safety

The inherent uncertainties in measuring activity, and estimating the radiation absorbed dose for unsealed sources is so large, that to protect against a serious overdose, administered activity is limited. This is not radiation dose in the classical sense!

Dosing for radiolabeled therapeutics is similar to chemotherapy, where systemic toxicity is limiting, not like radiation therapy where a specific target dose is calculated.

First step in improving radiolabeled therapy is to accurately assay the administered activity!

Which brings us back to the dose calibrator!

How can you calculate radiation absorbed dose, when administered activity is not known.

Regulatory requirement (1)

10 CFR Part 35.60 Possession, use, and calibration of instruments used to measure the activity of unsealed byproduct material.

(a) For direct measurements….. a licensee shall possess and use instrumentation to measure the activity of unsealed byproduct material before it is administered to each patient or human research subject.

(b) (1) A licensee shall calibrate the instrumentation ….in accordance with nationally recognized standards or the manufacturer's instructions.

Regulatory Requirement (2)

- 10 CFR Part 35.63 Determination of dosages of unsealed byproduct material for medical use.
  - (a) A licensee shall determine and record the activity of each dosage before medical use.
  - (b) (1) Direct measurement of radioactivity;
  - (c) (1) Direct measurement of radioactivity;
  - (d) "……may not use … if the dosage differs from the prescribed dosage by more than 20 percent."

Accuracy

(a) "……may not use … if the dosage differs from the prescribed dosage by more than 20 percent." –Nuclear Regulatory Commission

(b) 5% - International Atomic Energy Agency

(c) 10% American National Standards Institute

(d) USP General Chapter 821 – Use "authentic" reference sources.

(e) ~ 5% - American Association of Physicists in Medicine Report 181 (June, 2012)

One state requirement

The licensee shall follow all of the U.S. Food and Drug Administration (FDA) requirements.

This state requires the licensee to comply with the drug label requirements. Although the intent is to ensure good practice, this has the potential to cause regulatory and practice of medicine conflicts.

The Selection, Use, Calibration, and Quality Assurance of Radionuclide Calibrators Used in Nuclear Medicine*

Electronics	Reference check source
Clock accuracy	Accuracy
Voltage	Reproducibility
Zero	Linearity
Background	Supplier Equivalence

*American Association of Physicists in Medicine (AAPM) Task Group Report 181, June, 2012.

United States Pharmacopeia (USP)

- Geometry
- Background
- Statistics
- Counting losses
- Carrier
- Radiochemical purity

•Radionuclidic Purity
•Labeling
•Identification and Assay of radionuclides
  –Instrumentation
  –Identification
  –Impurities
  –Comparison with calibration Standard

Reference Standards

- Radiation detection requires traceability to a national standard- often this implies the National Institute of Standards Technology (NIST)
- Primary standards- traceable directly to NIST
- Secondary Standards- traceable to primary standards

With all of this information and technology, and qualified professionals, why do we truly not know what patients are administered when using unsealed radioactive sources?

How do we ensure the patient's administered activity is correct?

Simply measuring activity in a dose calibrator does not constitute a calibrated measurement!

Some therapeutics are only calibrated by the manufacturer.

Are sites capable of accurately (1) calibrating or (2) verifying the activity of a known radionuclide?

What does calibration mean? A quality control test or measurement is not a calibration!

Should every clinical dose be verified on site?

- Is manufacturer's certification sufficient?
- Is nuclear pharmacy's certification sufficient?
- What is responsibility of site?

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Future Dose Verification Challenges

- Ra-223, an alpha emitter currently undergoing clinical trials in the U.S. will present some interesting challenges to validation and therapeutic dosimetry.
- FDA approved therapeutic beta emitters such as I-131 and Y-90 continue to raise dosimetry challenges.
- Even for diagnostic radiolabeled drugs, activity calibration standards need to be readdressed to move the field forward.

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In Closing: Two basic questions

- Does the definition of a dose calibrator need to be updated?
  - Traceability to a national standard.
  - Role and validity of correction factors such as energy, geometry, solution and vial attenuation.
  - Are detector make and model really sufficient?
- Should on site verification via a measurement always be performed prior to radionuclide administration?

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Acronyms

- Bq – Becquerel
- CFR – Code of Federal Regulations
- Gy - Gray
- I-131 – Iodine-131
- mCi - milliCurie
- Ra-223 – Radium-223
- Y-90 – Yttrium-90

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AAPM REPORT NO. 181

The Selection, Use, Calibration, and Quality Assurance of Radionuclide Calibrators Used in Nuclear Medicine

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Objectives

To develop guidance on the selection, use, calibration, and quality control of radionuclide calibrators for use in nuclear medicine. The calibrators addressed are pressurized, well-type, ionization chamber radionuclide calibrators for measuring the activity of x- and gamma-ray emitting radionuclides, positron emitters, and medium to high-energy beta emitters.

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1. Introduction

1.1 Purpose

This document is designed to provide guidance on the selection, use, calibration, and quality assurance of radionuclide calibrators for use in nuclear medicine for the quantification of the activity of known radionuclides.

1.2 Scope

The scope of this document has been limited to radionuclide calibrators that incorporate pressurized, well-type ionization chambers for measuring the activity of x- and gamma-ray emitting radionuclides, 511 keV annihilation photons, and medium- to high-energy beta emitters.

2. Background

2.1 Assay of Radioactivity for Clinical Use

The accurate assay of activity prior to administration is one of several important processes required to assure that patients receive the correct radiopharmaceutical dosage. Assuming that the treatment or diagnostic study is appropriate and the prescribed radiopharmaceutical is being administered via the prescribed route to the correct patient, other processes include the determination of the appropriate activity to be administered and the successful administration of that activity.

Radionuclide or dose calibrators are the instruments most often employed to assay the activity of a radioactive material prior to clinical use. The objective of the assay is to help assure that the patient receives the minimum absorbed dose compatible with obtaining a high-quality diagnostic image or with achieving a desired therapeutic outcome.[1]

2.2 Selection of Patient Dosages

2.2.1 Patient Dosages

In the United States, physician "authorized users" specify the activity or range of diagnostic activities to be administered to a patient in either a written directive or in the directions for diagnostic procedures (e.g., a list of prescribed dosages or in a written protocol).[2] Typically, the activities are pragmatic values that are based upon accepted practice. Dosages may be adjusted for patient size (e.g., pediatric patients and heavy adults) or condition (e.g., pregnancy). The values can vary widely among nuclear medicine facilities. Therapeutic dosages may be based on an established protocol or calculated based upon patient-specific data.

2.2.2 Diagnostic Reference Levels

For diagnostic studies, to assure that patient absorbed dose is commensurate with the clinical purpose, the use of Diagnostic Reference Levels (DRLs) has been recommended for nuclear

medicine.[3] Several countries have both established and implemented numerical values for administered activity;[4] however, in the United States, national DRLs have not been set and are presently not required by regulatory agencies. Reference levels for radiopharmaceutical therapies are considered inappropriate.[5]

2.2.3 Nuclear Regulatory Commission

In the United States, both the Nuclear Regulatory Commission (NRC) and the Agreement States regulate the possession, use, and quality control of radionuclide calibrators. Agreement State requirements typically reflect those of the NRC but may not be identical. The regulations quoted in this document represent the current (time of publication) NRC regulations.

Diagnostic and therapeutic dosages go through several stages from prescription to delivery. They originate as an oral or written prescribed dosage. Then, during preparation they are measured and become the assayed dosage and, eventually, they become the delivered dosage. Prescribed dosage is defined as "the specified activity or dosage range as documented in a written directive or in accordance with the directions of the authorized user physician."[2] A licensee must determine and record the activity of each unit or non-unit dosage before medical use (see section 2.3) and (unless otherwise directed by the authorized user) may not use a dosage if the dosage does not fall within the prescribed dosage range or if the dosage differs from the prescribed dosage by more than 20%. This requirement includes dosages measured in a radionuclide calibrator. The delivered dosage might differ from the prescribed dosage and/or the assayed dosage.

2.2.4 Food and Drug Administration

The Food and Drug Administration (FDA)–required radiopharmaceutical labeling (package insert) typically includes manufacturer-recommended dosages or dosage ranges. Dosage recommendations are based upon supporting data indicating a safe and effective dosage. There can also be recommended dosages or dosage ranges for both adult and pediatric patients as well as recommended dosage adjustments for patient conditions (e.g., for renal disease and other conditions such as low platelet counts). However, package inserts may not reflect current experience and/or technology and the recommended dosages may no longer be current. Investigational studies using radiopharmaceuticals may require FDA approval through the Investigational New Drug (IND) or Radioactive Drug Research Committee (RDRC) process. Radiopharmaceutical dosages are approved as a part of these processes.

2.3 Requirements for Dosage Assay

2.3.1 Nuclear Regulatory Commission

The NRC addresses the assay of radioactive drugs for manufacturers in Title 10 CFR Part 35[2] and CFR Part 32.[6] Part 32 regulates the manufacture, preparation, or transfer for commercial distribution of radioactive drugs containing byproduct material for medical use under Part 35. Part 35 addresses the assay of radioactivity for clinical use and contains several important definitions, including, that of a unit dosage. A unit dosage is defined as a "dosage prepared for medical use for administration as a single dosage to a patient or human research subject without further

manipulation of the dosage after it is initially prepared." Therefore, a dosage withdrawn from a multi-dose vial or withdrawn from a vial containing a single dosage is not a unit dosage (as defined) because it has been further manipulated. In addition, a dosage prepared as a unit dosage that is altered (e.g., activity removed) is no longer a unit dosage by definition.

Part 35 requires that a licensee determine and record the activity of each unit or non-unit dosage before medical use. The determination may be made by direct measurement. For direct measurements, the regulations require instrumentation to measure the activity of unsealed byproduct material before it is administered. The instrumentation must be calibrated in accordance with nationally recognized standards or the manufacturer's instructions. For unit dosages, the NRC also allows the activity to be determined without measurement by decay correction based on the activity or activity concentration provided by an approved supplier. For non-unit dosages, the activity may also be determined by a combination of volumetric measurements and mathematical calculations based on the measurements of an approved supplier. However, this Task Group recommends that all dosages be assayed prior to administration. As noted by the National Council on Radiation Protection and Measurements (NCRP), "good practice requires that all individual doses be checked to minimize the possibility of error."[7]

2.3.2 Food and Drug Administration

The FDA recognizes the radionuclide dose calibrator[8] as a device intended to assay radionuclides before administration to patients. The FDA typically requires package inserts to include a general statement indicating that patient dosages should be measured immediately prior to administration. The FDA guidance document on good manufacturing practice for positron emission tomography (PET) drugs recommends that a radionuclide calibrator be used to measure the radioactivity of PET drugs.[9]

The United States Pharmacopeia/National Formulary (USP-NF)[10] contains both general chapters and monographs that include references to the necessary use of radionuclide calibrators as a part of the preparation and use of radiopharmaceuticals for diagnosis and therapy. General chapters numbered below 1,000 are enforceable by the FDA. USP General Chapter <821> "Radioactivity" is the most relevant to the use of radionuclide calibrators and specifically requires the use of instruments necessary for the accurate identification and assay of radionuclides. The ionization chamber is identified as an instrument that may be employed for this purpose. General Chapter <821> also addresses the calibration and quality control of radionuclide calibrators including a recommendation that all calibrations be performed using "authentic" reference sources of individual radionuclides rather than interpolation from an energy-response curve.

2.4 Accuracy of Dosage Assay

2.4.1 Assay Accuracy

In most countries, the standard of good practice is for the administered dosage to be within ±10% of the prescribed dosage. To help achieve this, the International Atomic Energy Agency (IAEA) recommends a calibrator accuracy of ±5%[1] and the American National Standards Institute (ANSI) recommends an assay accuracy of ±10%.[11]

This Task Group recommends that the assayed dosage be within ±10% of the prescribed dosage for diagnostic dosages and ±5% for therapeutic dosages when practicable. For I-131 liquid solutions, ±5% is readily achievable; however, for I-131 in capsular form ±5% of the prescribed dose at the time of administration may be problematic since the dosage cannot be adjusted. For pure beta emitters ±5% may be more difficult to achieve. In addition, for liquid therapeutic dosages, potential residual activity in the source container or delivery lines should be assayed immediately post-administration to assure that the proper dosage has been delivered.

2.4.2 Nuclear Regulatory Commission

The NRC[2] requires that (unless otherwise directed by the authorized user) a licensee not use a dosage if the dosage does not fall within the prescribed dosage range or if the dosage differs from the prescribed dosage by more than 20%. The latter is typically interpreted to require that assayed dosages be within at least ±20% of the prescribed dosage. However, as noted above, this Task Group recommends narrower limits as the standard of practice (see section 2.4.1).

2.5 Responsibility for Accurate Dosage Assays

From a regulatory standpoint, the licensing body holds the licensee ultimately responsible for accurate assays; however, there are key individuals who (under the license) share (to different degrees) responsibility for the proper assay. The licensee is required to identify authorized individuals who supervise the day-to-day use of radioactive materials under the license. These include physician-authorized users and authorized nuclear pharmacists.

Nuclear medicine technologists are typically not listed on a license and work under the supervision of a physician authorized user or an authorized nuclear pharmacist; however, they are often the "final filter" assuring that the correct dosage is administered to the correct patient. Other individuals (including nuclear medical physicists and medical health physicists) may have assay responsibilities but are not typically listed on a license and also may work under the supervision of the physician authorized user or an authorized nuclear pharmacist.

Radionuclide calibrator manufacturers bear some responsibility for facilitating accurate assays. To meet this responsibility they must provide accurate calibration settings for well-defined, reproducible source and chamber geometries. Ideally, the calibration settings should be for the source geometries that are used clinically. This Task Group recommends that calibrator manufacturers provide a declaration of performance (see section 9.1) with each radionuclide calibrator that clearly identifies the uncertainty of their calibration settings (preferably traceable to National Institute of Standards and Technology [NIST]). The manufacturer should provide the methodology used to derive the calibration settings and for what chamber and source geometry(ies) they may be applied. Most users are not aware that calibration settings are often calculated using response-energy curves (see section 4.3) and that the measurements or calculations may be based on source geometries that differ significantly from the clinical source geometries. In addition, commercial nuclear pharmacies (including radiopharmaceutical manufacturers) need to work closer with licensees to help assure accurate assays for clinical geometries.

3. Assay Systems

3.1 Absolute Assay Systems

An assay system may be designated as "absolute" if the measurement produces a disintegration rate (e.g., disintegrations per second) that is independent of a calibration factor or of a reference to some other standard of activity. Absolute assay systems include established methods such as $4\pi\beta^{-}\gamma$ coincidence counting.[12] Knowing the disintegration rate per unit mass and the mass of a master solution, a primary standard can be prepared and knowing the MBq/g (megabecquerels per gram) of the primary standard and the pA/g (picoampere per gram) response of the radionuclide calibrator, one can derive a calibration factor (pA/MBq) for well-defined measuring geometries.

3.2 Radionuclide Calibrators

Absolute assays are not necessary in most clinical situations, assuming radioactivity is assayed using an instrument that has been calibrated relative to some traceable standard of known accuracy. The typical instrument for assaying radiopharmaceuticals is the pressurized, well-type ionization chamber. These instruments are capable of providing radioactivity measurements to within the required accuracy levels (for clinical activities) when properly calibrated, operated, and maintained. These systems are called radionuclide calibrators (IEC, NPL [International Electrotechnical Commission, National Physical Laboratory]) or radionuclide dose calibrators (FDA) or radionuclide activity calibrators (NIST) or dose calibrators (common usage, USP and ANSI). However, since the word "dose" is broadly used to refer to units based upon the energy absorbed per mass of irradiated material, the term "radionuclide calibrator" is used in this publication.

For a medical facility, a radionuclide calibrator is typically purchased pre-calibrated by the manufacturer for commonly used radionuclides. Calibration coefficients (typically available as calibration settings on the radionuclide calibrator console) are provided for specific sample configurations (e.g., glass vials and/or plastic syringes). These calibration settings are initially determined by the manufacturer for a master system or a typical production system by direct measurement using primary or traceable standard sources, or they may be calculated using response-energy curves obtained using standard sources and published decay schemes. The calibration settings are then transferred to the production systems. Radionuclide calibrators may also be calibrated at the medical facility using commercially available primary standards or standards that are traceable to primary standards. Radiopharmaceutical manufacturers or commercial nuclear pharmacies may also provide calibration settings traceable to NIST standards.

3.3 Secondary Standard Radionuclide Calibrators and Reference Radionuclide Calibrators

A radionuclide calibrator that has been directly calibrated using primary standards may be used to provide secondary standard sources for calibrating production radionuclide calibrators (field instruments). A calibrator that is used to provide secondary standards is called a secondary standard radionuclide calibrator (SSRC).[13] Theoretically, any reliable field instrument that

has been calibrated using primary standards traceable to a national standards laboratory can serve as an SSRC for specific source geometries if it is properly it operated, maintained, and undergoes proper quality control. A reference radionuclide calibrator (RRC) is a radionuclide calibrator that has been calibrated using traceable secondary standard sources, and it may also be used to calibrate field instruments.

3.4 Accuracy of Radionuclide Calibrators

Although radionuclide calibrators appear to be one of the less complicated pieces of medical equipment, their measurement sensitivity for a particular radionuclide is a function of many variables, each of which may lead to significant errors.[14] However, as noted by Zimmerman and Cessna, "while these devices are not appropriate for metrology applications, they are capable of providing radioactivity measurements to within the accuracy levels required by radiopharmaceutical manufacturers and clinical users when properly used and maintained."[15] The standard of good practice in most countries is that the administered dosage should be within 10% of the prescribed dosage (see section 2.4.1). Therefore, given the other sources of error involved in the delivery of the dosage, radionuclide calibrators should introduce a measurement error of less than 10%.

For radionuclide calibrator field instruments, this Task Group recommends radionuclide calibrator accuracy within ±5% (at k=2 level) for photon emitters >100 keV and within ±0% (k=2) for photon emitters <100 keV.[17] For medium- and high-energy beta emitters, this Task Group recommends radionuclide calibrator accuracy within ±5% (at k=2 level) for low-energy beta emitters within ±10% (k=2).[17] Secondary standard radionuclide calibrators and reference radionuclide calibrators should be calibrated to within ±2% (at k=2 level) for photon emitters >100 keV and medium and high-energy beta emitters and within ±5% (at k=2 level) for photon emitters <100 keV and low-energy beta emitters.[17] Because licensees can use unit dosages obtained from approved suppliers without re-assay,[2] this Task Group recommends that these suppliers (e.g., radiopharmaceutical manufacturers and commercial nuclear pharmacies) calibrate and maintain their radionuclide calibrators as either secondary standard radionuclide calibrators or as reference radionuclide calibrators.

4. Radionuclide Calibrators: Pressurized, Well-Type Ionization Chambers

4.1 Basic Design and Operating Characteristics

Radionuclide calibrators are most commonly re-entrant (well-type) pressurized ionization chambers directly coupled to an electronic circuit that converts and displays chamber response (time-averaged ionization current) in units of activity. The principles of ionization chamber operation are well summarized in other publications.[12,16] In this document, basic design and those operating characteristic that affect calibration and day-to-day operation are discussed.

Radionuclide calibrators consist of an array of concentric cylinders with an axial symmetry in the vertical direction. The chamber wall is typically an aluminum alloy a few millimeters

thick. Variations in wall thickness are subject to manufacturing tolerances. The effect of variations in wall thickness depends upon the radionuclide and the container format. The chambers are sealed with a filling gas at high pressure. A sealed chamber eliminates the need for temperature and pressure correction and the high pressure increases detection sensitivity. Modern radionuclide calibrators have larger chambers that decrease (but not eliminate) the source positional dependence due to a longer longitudinal *z*-axis uniform efficiency or "sweet spot."

Saturation current is maintained using a stabilized high voltage (HV) supply that allows the accurate assay of up to several hundred gigabecquerels (GBqs) (several curies [Ci]) of activity for some radionuclides without significant ion recombination and space charge effect. System linearity (section 5.3) reflects these saturation characteristics of the ionization chamber. The probability of ion recombination and space charge effect increases with increasing activity and potentially results in a reduction in the ion current collected per unit activity leading to an underestimate of the assayed activity.

Calibrator electronics include an electrometer designed to measure a wide range of ionization current. System linearity also depends upon the linearity of the electrometer. The current produced per unit activity (MBq) for common radionuclides ranges from tens of femtoamperes (fA) for high-energy beta emitters up to tens of picoamperes (pA) for high-energy, high-yield photon emitters. High-activity assays can involve microamperes (μA) currents. The accuracy of the electrometer depends upon the type and quality of the electrometer and the accuracy of the standard reference sources used to calibrate the electrometer. Auto-ranging electrometers have replaced mechanical range switching electrometers eliminating one potential (mechanical) source of nonlinearity; however, calibrators may still exhibit some range-changing nonlinearity.[17] Typical commercial electrometers used for radionuclide calibrators have a nominal accuracy of about ±1% to 2%.

Chamber shielding is used to reduce the effect of local environmental radiation and to reduce unnecessary operator exposure. Most commercial calibrators come with inherent chamber shielding, but additional shielding can be purchased to either reduce chamber background in a high background environment or to reduce operator exposure. Backscatter and the emission of lead x-rays from shielding can alter the response of the chamber and affect the accuracy of the calibration settings. Radionuclide calibrator manufacturers should confirm that the calibration settings provided accurately reflect the contributions from the supplied chamber shielding (both for inherent and additional shielding). The source holder provided with the calibrator and the plastic chamber liner are important parts of the assay system. Manufacturer-supplied calibration settings are measured or calculated for sources in a specific source container and source volume positioned in the chamber using the source holder. Since chamber sensitivity varies in both the horizontal and vertical directions, proper use of the supplied source holder with the liner in place is essential. In addition, current production radionuclide calibrators incorporate microprocessors that allow additional quality control tests to be performed and digital display devices have replaced analog devices. Radionuclide calibrators have no intrinsic photon energy discrimination capability; they are not spectrometers and the settings do not restrict the measurements to specific photon energies to the exclusion of others. All settings will display an activity reading when sufficient activity is positioned in the chamber; however, only the setting for the specific radionuclide being measured will potentially yield the correct activity.

While radionuclide calibrators have many features in common with un-pressurized re-entrant (well-type) ionization chambers, radionuclide calibrators should not be used for the calibration of sealed-sources containing radionuclides for (non-microsphere) brachytherapy.[18]

4.2 Calibration Coefficients

A calibration coefficient is the coefficient used to convert the measured ionization chamber current to a nominal activity. The magnitude of a calibration coefficient depends upon the radionuclide, the physical characteristics of the ionization chamber (inner chamber wall thickness, gas pressure, chamber design, and operating voltage) and the source geometry (container type, container wall thickness, source volume, and position of the container in the chamber). Additional components common to commercially available radionuclide calibrators also influence the measured current, including lead shielding, the sample holder, and the removable liner. Table 1 lists calibration coefficients for the NPL secondary standard ionization chamber for a number of commonly used radionuclides.[19] Calibration coefficients are often referred to as calibration factors.

For a given radionuclide, the response of the chamber depends upon type of decay, particle(s) energy, and the decay scheme of the radionuclide. Source volume affects chamber response due to attenuation and/or chamber position. For most commercially available radionuclide calibrators, calibration coefficients (e.g., in pA/MBq) are available indirectly as calibration settings applied using buttons, dials, numeric keypads, etc. These calibration settings are initially determined by the calibrator manufacturer and are typically assigned by radionuclide. However, it is the response of the chamber to a given radionuclide in a specific source geometry that is correlated with a particular setting. Thus, in order to obtain an accurate activity reading for a selected radionuclide, calibration settings must be determined for that radionuclide in the specific geometry being used.

Table 1. Examples of Calibration Coefficients (Vial) from the NPL Secondary Standard Radionuclide Calibrator

Radionuclide (pA/MBq)	Calibration Coefficient
P-32	0.03518
Y-90	0.0721
Tl-201	0.886
Tc-99m	1.240
Ga-67	1.565
I-123	1.721
I-131	4.073
I-131 (capsule)	4.053
In-111	4.129
F-18	10.39

Commercially available radionuclide calibrators are typically provided with calibration settings that can be used for specific containers and volumes of solution. When calibration settings are based upon glass vials' geometry, measurements made using plastic syringes can be significantly higher for radionuclides whose decay includes lower energy photon emissions.[20,21] When calibration settings are based upon plastic syringes, the opposite may be true. Calibration settings are typically determined by measurements using traceable reference standards and/or (by the calibrator manufacturer) by calculation using the calibrator's response-energy curve.[22] Calibration settings may also be obtained from radiopharmaceutical manufacturers, commercial nuclear pharmacies, or measured in-house using national standards or sources traceable to national standards. In the United States, national standards are available from NIST[23] and are called Standard Reference Material (SRM). NIST-traceable standards are available from several commercial sources. Some commercially available radionuclide calibrators (manufactured abroad) may be calibrated using standards traceable to the other primary standards laboratories (e.g., NPL, United Kingdom; PTB[†] Germany; LNHB[†], France).

4.3 Response-Energy Curves (Photons)

A typical response-energy or sensitivity curve for an aluminum alloy wall chamber is shown in Figure 1. It is modeled after a commercially available radionuclide calibrator's sensitivity curve.[24] Chamber output due to 3.7×10^{10} photons of energy E is normalized to the output of a reference radionuclide (in this case, Co-60). To generate the curve, a limited number of calibration coefficients are measured using standard reference sources over the range of energies of interest. The chamber response due to specific photons emitted by the radionuclides is calculated, normalized to a reference radionuclide, and plotted to yield the response-energy curve. Using the resulting response-energy curve, calibration coefficients for other radionuclides can be calculated using published decay schemes.

For aluminum-walled chambers, photons with energies below approximately 13 keV are stopped before they reach the sensitive volume of the chamber. The actual cutoff depends upon the source volume; the source container wall material and thickness; and the thickness of the source holder, plastic liner, and chamber wall. These thicknesses will vary according to system design and manufacturing tolerances. As seen in Figure 1, from a low-energy threshold, ionization current increases rapidly and then abruptly decreases, yielding a peak centered at approximately 50 keV. The peak results from the competing effects of increased photon transmission through the source, source container, plastic source holder, plastic liner, and chamber wall (as their photoelectric cross sections decrease rapidly), combined with the eventual decrease in photon interaction with the chamber sensitive volume (as the chamber's photoelectric cross section decreases). Compton scatter becomes the most probable interaction at approximately 50 keV. Above 200 keV Compton scatter dominates and sensitivity increases approximately linearly with increasing photon energy. Thus, detection efficiency is low at low energies, peaks around 50 keV, reaches a minimum near 200 keV, and increases linearly as energy increases.

[†]PTB = Physikalisch-Technische Bundesanstadt; LNHB = Laboratoire National Henri Becquerel.

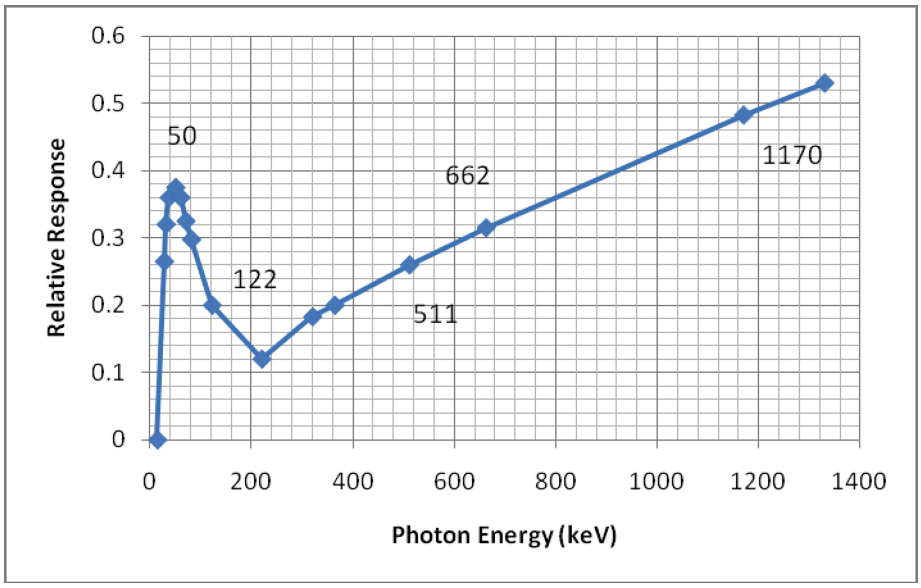

Figure 1. Example of commercial radionuclide calibrator efficiency or response-energy curve (relative to Co-60).

5. Sources of Assay Errors

5.1 Plug and Play

It has been common practice to use a radionuclide calibrator "as is" from the manufacturer, i.e., the calibrations settings for a specific radionuclide are assumed to be dependent only the radionuclide and not on the radionuclide in combination with other factors; including the source container, source volume, and source position in the chamber. Individuals in medical facilities or in commercial nuclear pharmacies who use radionuclide calibrators on a daily basis may not fully understand the calibrator's operating characteristics and may not have read and/or understood the operating manual.

Ideally, a radionuclide calibrator should come calibrated for each radionuclide and sample configuration to be used in clinical practice. However, this is not the case and calibrations are typically derived for one container type, a specific source volume, and a specific chamber position. They are initially measured or calculated for a manufacturer's master or typical production system. The calibrations are then transferred to each field instrument using limited source measurements and an algorithm that relates dial settings to calibration factors. Calibrations provided by the calibrator manufacturer may be sensitive to small changes in both source and positional geometries and any change may affect the calibration coefficients and, thus, the assay to some degree. It is up to the user to either demonstrate that the change is not significant (<5%) or, if significant, new calibration settings, calibration coefficients, or correction factors need to be derived and applied.

For example, an NPL report[25] summarized the test results from nine commercial radionuclide calibrators. The instruments were used "as is" from the manufacturer to assay nine different photon-emitting radionuclides dispensed into common formats. Only two of nine calibrators

assayed eight to nine of the radionuclides within the 5% accuracy objective for a range of radionuclides and sample formats (the other radionuclides assayed within 8%). The remaining calibrators exhibited systematic discrepancies for all the radionuclides tested. Many of the calibrators assayed common nuclides accurately in vial formats and less accurately in other formats. Some radionuclides were more difficult to assay than others (see section 5.4.1). For example, radionuclides that emit lower energy photons (e.g., characteristic x-rays) that contribute significantly to the measured current are more difficult to assay accurately (e.g., I-123 and In-111). Radionuclides that emit higher energy photons (photons >100 keV) typically are easier to assay accurately (e.g., Tc-99m and I-131).

In a study that assessed the accuracy of the hospital measurements of Tc-99m activity,[26] the accuracy, in a large majority of cases, was better than 5%. Specifically, 2% of the measurements were within 2% of the calibrated activity, 96% were within 5%, and only one measurement was greater than 10%. In the majority of cases the manufacturer's recommended dial setting was used. However, it should be noted that the measurements were made using vial geometry on instruments that were calibrated for vial geometry. The study does not reflect the errors introduced when activity is measured in a syringe format on an instrument calibrated using a vial format.

It appears that I-131 sources are not particularly sensitive to container differences and any differences may be due to variations in geometry within the chamber, e.g., the syringe will not be in the center of the chamber.[18,19] However, even high-energy photon emitters demonstrate some container differences. For example, using an NIST standard of F-18, Cessna et al.[27] obtained two different calibration settings, one for a 5 milliliter (mL) NIST ampoule and the other for 1 mL of solution in a 3 mL BD syringe. Both assays were significantly different (+6.4% and +8.9%, respectively) from the assays obtained using the manufacturer-recommended calibration setting.

In the ANSI standard[11] several common sources of error or uncertainty in the assay of radionuclides with ionization chambers are identified. In addition, NPL Report No. 93[17] identifies several additional sources of uncertainty. Table 2 is a list of common sources of error or uncertainty based upon these documents.

Radionuclide calibrators are not absolute assay systems. They are calibrated either directly or indirectly using standard reference sources traceable to absolute assay systems. At best, the accuracy of the calibration corresponds to the accuracy of the standard reference sources used for the initial calibration. These sources are available with standard uncertainties (at k=2 level) that range typically from 1% to 2% depending on the radionuclide.[17] For calibration settings derived using response-energy curves and published decay schemes, the uncertainty may be greater.

5.2 Source Geometry

Source geometry is probably the most significant source of assay errors,[12] specifically, the difference between the container used to obtain the initial calibration settings and the containers used to assay dosages in clinical practice. Radionuclide calibrator manufacturers typically calibrate their instruments using a national standard vial (e.g., the NIST SRM borosilicate-glass ampoule) or a specific multi-dose vial.[18] Ideally, the geometry of the standard source should be identical to the geometry of the source being assayed. If the source geometry is not identical, the

Table 2. Common Sources of Uncertainty in the Assay of Radionuclides with Ionization Chambers

1.	Errors in calibration of standard reference sources
2.	Errors in calibration by interpolation using "master" chamber response-energy curve and published decay schemes as extrapolated to "field" instruments
3.	Variation in "field" instrument wall thickness and chamber gas pressure
4.	Backscatter from chamber shielding
5.	Inherent accuracy and linearity of electronics, including range changing errors (with and without with auto-ranging electrometers) and rounding or truncation errors
6.	Ion pair recombination with high-activity sources
7.	Variations in radiation background with low-activity sources
8.	Differences between calibration containers and sample containers
9.	Variation in attenuation due to variations in sample containers' wall thickness or material and sample volume
10.	Sample position in the chamber (including changes in sample volume)
11.	Solution density and homogeneity are potential problems but typically not significant. Non-homogeneity due to settling can be a problem with microsphere dosages

error in the measurement should be quantified and, if significant, either a new calibration setting determined or a correction factor applied.

Some calibrator manufacturers recommend calibration corrections for syringes, but the suggested values may be significantly underestimated. The situation is complicated in that there is no standard syringe and the type of syringe, volume of solution, and needle length used to assay dosages vary and may have a significant effect on the result.[19,20] For a given syringe type, manufacturing tolerances vary and calibration settings among manufacturers and for batches of syringes for the same manufacturer may vary significantly.

Vial differences can also introduce assay errors. A measurement in a multi-dose vial that is different from the vial used to calibrate the system may require a correction factor or a new calibration coefficient.[18] In the United States, there is no agreed upon multi-dose vial, and radiopharmaceutical manufacturers and nuclear pharmacies provide their products in a variety of vial configurations and the vial production tolerances (e.g., wall or vial bottom thickness) may vary significantly. Thus, it is necessary for the user to be aware of this source of assay uncertainty and to ascertain if the error(s) introduced are significant.

Position of the source in the chamber introduces additional uncertainty if different from that of the reference standard at calibration. Source holders provided with the calibrator generally ensure that the vertical position of the source is maintained. However, vertical and horizontal changes in source position within the holder (e.g., syringe angle in holder and syringe height and

source volume) may affect chamber response. Source settling and the subsequent change in source position can also affect chamber response.

Typically, doses can be assayed accurately independent of the sample size if the chamber well is much larger than the sample size and the source is located in the center of the well. However, even with the current production calibrators and their large chamber volumes, radionuclide calibrator manufacturers need to better define the location and size of the optimum measuring region or "sweet spot." In a paper by Santos et al.[28] the authors recommend the characterization of two important chamber regions: the first region corresponds to the locations where the deviation from the maximum efficiency is less than 5% and the second where it is less than 10%. The authors suggest that these parameters can be used for source position optimization, for the characterization of calibrators during acceptance testing, and as a tool for quality control testing. Axial response can also include an energy-dependent component of variation.

5.3 Linearity

Calibrator response is considered linear if the ratio of the measured response to the predicted response remains constant over the range of current inputs for which the calibrator is designed. System linearity reflects both the linearity of the ionization chamber (saturation characteristics) and the linearity of the electrometer. Ideally, linearity would be tested for each radionuclide at the upper range of the proposed administered activities.[11] However, this is often impractical and most calibrators are tested with Tc-99m or with F-18 (for PET-only facilities). The current produced per unit activity varies with the radionuclide. For F-18, Tc-99m, and I-131 it is roughly proportional to the air kerma rate constants (for photons >20 keV); thus, Tc-99m yields approximately 3 times less current than I-131 and approximately 8 times less current than F-18 per unit activity.

For medical facilities that elute Mo-99/Tc-99m generators, the highest activity assayed is typically the initial elution of a new generator, and this elution yields the highest measured current. For a facility that purchases bulk Tc-99m pertechnetate for in-house compounding, these bulk activities will typically produce the highest current. For facilities that use only unit diagnostic dosages purchased from an outside source, the highest assayed diagnostic dosage will produce the greatest current. If however, high-activity I-131 therapeutic dosages are also administered at these facilities, these dosages, typically, will produce the highest current input.

The IEC[29] and the NPL[17] recommend that linearity be measured over the entire range of activity for which the calibrator will be used. ANSI[11] and the IAEA[1] recommend that calibrators be checked over the range of use starting at the highest activity administered. The IAEA[1] recommends that linearity be ascertained over the range of use between the maximum activity administered and 1 MBq. The qualification "over the range of use" was incorporated into an earlier version of 10CFR35[2] regulations. The IAEA,[1] IEC,[29] and European Association for Nuclear Medicine (EANM)[30] recommend routine linearity testing on an annual basis. The recommendations of this Task Group for range of activity and frequency of the testing are found in the appendix.

5.4 Problem Radionuclides

5.4.1 Low-Energy Photon Emitters

The magnitude of the low-energy peak in the response-energy curve (Figure 1) has important assay implications. A number of commonly used radionuclides emit relatively abundant characteristic x-rays in addition to their principal photons. The characteristic x-rays from these radionuclides have energies that fall within the peak and potentially contribute a large component to the ionization current. If the source container is glass, the x-rays may be highly absorbed in the glass wall. If the container is a capsule or plastic syringe, a significant number of the x-rays will penetrate to the sensitive volume of the chamber. As noted in section 4.2, radionuclide calibrators whose calibrations are based upon measurements made in glass vials will assay high when measuring these low-energy photons in capsule form or in a plastic syringe and, for calibrators whose calibrations are based on syringe geometry, the reverse is true.

Calibration settings designed for glass vials give increasingly inaccurate results (overestimation) in less attenuating source geometries as the mean effective energy of the photon emissions decreases. I-125 (not commonly used in clinical nuclear medicine) exhibits a difference between 10% to 80% from the true activity; correction factors of 20% to 60% may be required for I-123 and correction factors of 15% to 30% may be required for In-111 solutions,[19,20] depending on the syringe used. Other low-energy photon emitters with similar correction factor problems include Xe-127, Xe-133, Tl-201, and Yb-169.

Thus, low-energy photon sources (i.e., less than approximately 100 keV) may be assayed incorrectly unless care is taken in the selection of the source container.[11] Significant attenuation may occur in the container, the source holder, or the interior wall of the calibrator chamber. Some radiopharmaceutical manufacturers provide dial settings for I-123 in capsule and syringe configurations and In-111 in a syringe format. However, it must be assumed that small differences between the radiopharmaceutical manufacturer's calibrator and the medical facility's calibrator occur (even for the same model calibrator) due to manufacturing tolerances (e.g., chamber wall thickness), and calibration settings should be established by actual measurement.

The problem of unequal attenuation of low-energy photons (e.g., in container and chamber walls) is minimized with a thin copper insert.[31–33] The copper insert (approximately 0.6 to 1 mm thick) absorbs most of the low-energy photons and a smaller percentage of the higher-energy principal photons. Using a traceable reference source, the setting for the radionuclide can be recalibrated with the copper insert in place. Thus, measurements are relatively independent of container and chamber wall effects for the low-energy photons. The use of a copper insert has been recommended for use with I-123 and In-111.[34] Copper inserts are commercially available.

5.4.2 Beta Emitters

Sufficient activities of several clinically important beta emitters can be accurately measured in a radionuclide calibrator using the bremsstrahlung produced as the beta particles interact with surrounding materials. Laedermann et al.[35] demonstrated that most of the first bremsstrahlung interactions occur in the source (solution and container) followed by interactions with the chamber's aluminum wall (only significant for beta energies greater than approximately 2 MeV) and

at energies greater than approximately 2.5 MeV, direct ionization of the chamber sensitive volume dominates and may significantly distort assay results. The sensitivity of radionuclide calibrators for beta particles is only a fraction of the response for photon emitters and depends strongly upon the maximum energy of the beta particle. When measuring low-energy beta emitters, the background contribution may be significant and must be subtracted. For high-energy beta emitters direct interaction with the chamber sensitive volume may be a problem.[35,36] An example of a low-energy beta emitter used clinically is Er-169 (E_{max} = 0.35 MeV). Examples of medium-energy beta emitters are Sr-89 (E_{max} = 1.5 MeV) and P-32 (E_{max} = 1.7 MeV). A beta emitter with an E_{max} greater than 2 MeV is considered a high-energy beta emitter.

Le Blanc and Johnson[37] demonstrated that a reasonably accurate assay of P-32 solutions could be made using a commercial calibrator. However, the authors cautioned that P-32 calibration is very dependent upon the equipment and materials. They emphasized the need to independently assay P-32 solutions because of the large errors in supplier assays they had observed and because an independent assay of each dose administered reduces the possibility of error. ANSI[11] also cautions that when measuring beta-emitting radionuclides in a radionuclide calibrator, the container is extremely important and that measurements of the same radionuclide and activity will vary greatly with container composition (e.g., glass versus plastic) and wall thickness. The NRC has also addressed issues associated with the assay of pure beta emitters.[38,39]

Zimmer et al.[40] determined an accurate and sensitive calibration setting for P-32 that was linear over a wide range of activity (0.43 to 4.13 mCi). They observed that the assay accuracy was maintained within ±4%, indicating that syringe-wall absorption was also not significant. Zimmerman et al.[41] and Siegel et al.[42] evaluated the accuracy of 30 commercial radionuclide calibrators from three different manufacturers for Y-90–ibritumomab tiuxetan in 10-mL syringe geometry from 2.2 mCi to 38 mCi over a volume range of 3 to 9 mL. They concluded that (for this specific source geometry and activity range) only a single dial setting is required for a given manufacturer's radionuclide calibrator for accurate measurements and that volume correction is not necessary. The authors recommend that commercial nuclear pharmacies establish a Y-90–calibrated setting based on the NIST standard reference source so that each source supplied to a medical facility could be used as a secondary reference standard and each medical facility determine its own calibration setting based on the initial Y-90 activity received from the pharmacy. Alternatively, they recommend that the medical facility calibrate their calibrators using NIST-traceable activity source in the same syringe geometry. If available, a NIST-traceable calibration setting should always be used. If a traceable setting is not available, a decay corrected supplier's assay may be acceptable for unit dosages in the same geometry.[2] However, commercial nuclear pharmacies and radiopharmaceutical manufacturers should have traceable calibrations for all the dosages they supply.

5.4.3 Beta-Gamma Emitters

Beta emitters with significant gamma contributions behave like gamma emitters with the measurement efficiency mainly determined by the gamma component.[36] For these beta-gamma emitters, the beta component of the current is typically less than 1%. There are potential exceptions (e.g., Re-186 the efficiency is approximately 6%);[43] however, for most commonly used beta-gamma emitters the bremsstrahlung contribution from beta-gamma emitters should have minimal

effect on the accuracy of the assay. Sm-153 is a beta-gamma emitter with medium-energy betas of 640 keV (32%), 710 keV (30%), and 810 keV (18%) and a gamma of 103 keV (30%). The measurement efficiency is mainly determined by the gamma emission. However, due to the low energy of the gamma, assaying Sm-153 in a syringe geometry using a calibration factor obtained for glass-vial geometry may significantly overestimate (potentially >20%) the sample activity.

5.5 Radionuclidic Impurities

Many commonly used radiopharmaceuticals contain radionuclidic impurities that contribute to the measured ionization current. The magnitude of the chamber response depends upon the unwanted radionuclide(s), the percent radionuclidic impurity(ies), and the chamber response to the impurity(ies). Since an ionization chamber cannot inherently discriminate radionuclides by photon energy, it is difficult to adjust the assay for this contribution.

The main significance of the presence of radionuclidic impurities in radiopharmaceutical preparations is the associated absorbed dose received by the patient. In addition to additional absorbed dose to the patient, radionuclidic impurities may have other dose consequences, e.g., the presence of I-125 in the breast milk following the administration of I-123 sodium iodide. The presence of long-lived radionuclidic impurities in radioactive waste complicates waste disposal by radioactive decay. Users should be aware of the radionuclidic impurities that are present in patient dosages and their potential significance.

5.6 Operator Errors

Radionuclide calibrators are not complex instruments. However, they do need to be set up and operated per manufacturer's instructions and it is essential that those individuals who use radionuclide calibrators understand instrument operation and operating characteristics. It is the responsibility of the licensee to assure that individuals who use the instrument are properly trained. Quality control tests must be performed as required and appropriate action taken if a test fails. Operators need to understand that calibration coefficients are radionuclide and geometry dependent. Source holders must be used as instructed by the manufacturers and should be placed in the chamber properly, not physically altered, and replaced when broken. Source holders from different calibrator manufacturers should not be interchanged without verifying the accuracy of the calibration coefficients for the holder/calibrator combination.

6. Post-Assay Errors

6.1 The "Uncertainty Budget"

The error or uncertainty associated with the dosage assay is just one contributor to the difference between the prescribed dosage and the administered dosage. The logistics and techniques of dosage delivery also influence the amount of activity administered. Two potential significant sources of uncertainty are (1) the difference between the dosage calibration time and dosage administration time and (2) the residual activity remaining in the vial or syringe, the needle, or other parts of the delivery system post administration. However, despite these other

sources of uncertainty, it is important that the uncertainty associated with the accuracy of the dosage assay not dominate the overall recommended uncertainty budget; however, the user should be aware of these other sources of uncertainty and their potential magnitude. The stages and typical uncertainties involved in dosage delivery are listed in Table 3.

It is interesting to note that a number of the significant sources of uncertainty result in administered dosages that are less than the prescribed dosages. While the time to administration (see section 6.2) may lead to administered dosages that are greater than the prescribed dosage (i.e., for administrations at times pre-calibration); for dosages prepared in-house (versus unit

Table 3. Stages and Typical Uncertainties in Radiopharmaceutical Dosage Delivery

	Source of Uncertainty	Uncertainty
Prescribed Dosage		
↓		
Dosage Prepared	Technique/Human Error	Unknown
↓		
Assayed Dosage	Calibrator Accuracy	±5%–10%*
	% of Prescribed Dosage	±5%–10%*
↓		
Time to Administration	E.g., Tc-99m	0.2%/min
	E.g., F-18	0.6%/min
↓		
Residual Activity	E.g., Syringe-Needle Dead Volume	(–) ~6%
↓		
	E.g., Adsorption to Vessel Wall	(–) ~1%–30%
Administered Dosage	% of Prescribed Dosage	±10%*

*Recommended Maximum

dosages obtained from commercial nuclear pharmacies), radioactive decay most often results in less activity being administered. The errors due to residual activity (see section 6.3) result in less activity being administered and the assay of syringe using a calibration setting obtained using glass-vial geometry (see section 5.4.1) yields an overestimate of the activity in the syringe.

6.2 Time to Administration

For short-lived radionuclides such as Tc-99m and F-18, a small difference between the time of dosage calibration and the time of dosage administration can introduce a significant additional error. For Tc-99m, a 1-hour difference represents an 11% error and for F-18, 30 minutes results in a 17% difference. For Tc-99m, it is not uncommon for dosages to be administered at times greater than 60 minutes before or after the dosage calibration time, even in a hospital-based nuclear pharmacy.[44]

The transition to unit dosages supplied by commercial nuclear pharmacies (versus in-house production) presents additional logistical problems. For unit dosages supplied by a commercial nuclear pharmacy there may be a large difference between dosage calibration time and dosage administration time. This can result in routine over- or underdosing relative to the prescribed dosage. It can also lead to the application of fairly broad prescribed dosage ranges. This may make the adoption of DRLs problematic.

6.3 Residual Activity

Another potential significant source of error is the activity remaining in source containers and/or the associated injection sets. This source of error results in less activity being delivered than assayed. Most diagnostic radiopharmaceuticals are assayed and administered using syringes. The syringe-needle assemblies have a dead volume in which a portion of the solution remains. Dansereau and Methe[44] demonstrated that for a Tc-99m radiopharmaceutical approximately 6% of the activity remained in the syringe-needle post injection. In addition, significant activity (30% or greater) can adhere to the wall of the syringe barrel and activity can also remain in delivery lines even with proper flushing. Evaluation of radiopharmaceutical retention in syringes and injection sets should be performed as a part of routine quality control. By assuring compatibility of radiopharmaceuticals and injection devices, this source of error can be limited to a few percent.[45–48] Except for quantitative or semiquantitative imaging (e.g., F-18 FDG SUV[†] calculation), common practice does not account for this error in diagnostic dosage administration.

Some radionuclides tend to adhere to the glass walls of vials. Baker et al.[19] reported significant levels of activity (5% to 20%) adsorbed to the wall of P6 vials for commonly used radionuclides (Tl-201, Ga-67, and In-111). Carrier-free solutions of I-131 NaI (sodium iodide) can also adhere to glass walls and caps of containers. The error in dosage delivery can be significant (>20%) and can result in a "medical event."[2] For therapeutic dosages, the activity remaining in the source container[11] and delivery device should be measured immediately after administration before the patient is released and adjustments made as required by the responsible physician-authorized user. Wall adsorption can also be a problem with calibration standards, both when assaying the standard in the source container itself and when transferring activity to another container in order to establish new calibration factors for other source geometries.

[†] F-18 FDG SUV = F-18-fluoro-2-deoxy-D-glucose standard uptake value.

7. Calibration of Radionuclide Calibrators

7.1 Calibration and Traceability

Calibration is defined as "the process of determining the numerical relationship, within an overall stated uncertainty, between the observed output of a measurement system and the value, based on standard sources, of the physical quantity being measured."[11] For radionuclide calibrators, calibration is the process of determining the calibration coefficients or calibration settings for each radionuclide to be assayed. Calibration coefficients recommended by the manufacturers are presented as calibration settings for specific radionuclides; however, as noted in section 4.2, it is the response of the chamber that is correlated with that setting and chamber response depends upon a number of factors, including the radionuclide, the source geometry (including source volume and container type), and the chamber geometry (source position in the chamber). Therefore, in order to assure the correct assay of a particular radionuclide, the measurement must be made using the calibration factor appropriate for the radionuclides in the geometry for which the instrument was calibrated.

Traceability is defined as "the property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties."[17] For radionuclide calibrators, this means that calibration settings shall be traceable to national primary standards of radioactivity.

7.2 Radioactive Standard Sources

The ANSI standard[11] requires that calibrators be calibrated with identified radionuclide sources of known activity and established purity. ANSI nomenclature and definitions for radioactive standard sources from are used in this document, as follows:

1. **National radioactivity standard source.** A calibrated radioactive source prepared and distributed as a standard reference material by the U.S. National Institute of Standards and Technology.
2. **Certified radioactivity standard source.** A calibrated radioactive source, with stated accuracy whose calibration is certified by the source supplier as traceable to the National Radioactivity Measurements System.

7.3 Check and Mock Sources

7.3.1 Check Source

A solid radioactive source that is used for the determination of the long-term stability of an ionization chamber is called a check source. The source does not have to be a standard source. It should have a half-life greater than 5 years and the effects of any radioactive contaminants shall be such that the indication of the device over the period of 5 years would not deviate by more than 0.5% after decay correction for the known half-life of the principle radionuclide.[28] Cs-137 with its long half-life (30 years) or Co-60 (5.27 years) are the recommended check

sources. A certified radioactivity standard source could serve both as a check source of long-term stability and as a high-energy standard source for accuracy testing.

7.3.2 Mock Sources

Typically "mock" or "simulated" sources are not recommended for calibrating radionuclide calibrators because (although the principal photon energies may be similar) chamber response may not be the same. As noted by ANSI,[11] "simulated sources may be useful as a check source but are not recommended for activity-calibration purposes. Such sources, which are usually a mixture of long-lived radionuclides chosen to yield an approximation of the photon spectrum of the radionuclide they simulate, may not yield accurate calibration data in terms of ionization current." This reference to a mixture of long-lived radionuclides probably refers to a source such as "mock iodine" that was a mixture of Ba-133 and Cs-137. The mixture simulated the spectrum of I-131 and was used mainly with early NaI(Tl) crystal-based thyroid-uptake systems.

Mock sources used with radionuclide calibrators are typically single radionuclides and not mixtures of radionuclides. The most commonly used radionuclides include Co-57 and Ba-133. Their main use is as long-lived standards for accuracy testing at photon energies that are similar to clinical radionuclides. Along with the higher energy Cs-137 or Co-60 sources, they are used to test calibrator response over a broad energy range of the response-energy curve. However, the use of these sources to calibrate a radionuclide calibrator for the radionuclides they mock can lead to calibration errors. For example, using Co-57 activity to calibrate the Tc-99m setting or (even worse) Ba-133 activity to calibrate the I-131 setting will result in significant assay errors.

A more promising approach is the direct comparison of a standard source of a longer-lived radionuclide and a standard source of a clinical radionuclide to create a longer-lived traceable calibration surrogate whose activity is expressed in terms of an equivalent activity of the clinical radionuclide. For example, direct comparisons of Ge-68 and F-18 national standards have allowed the Ge-68 activity in an epoxy-based mock syringe geometry to be expressed in terms of a traceable equivalent F-18 activity with a relative combined standard uncertainty of about 0.9% in the same geometry.[49]

7.4 Calibrating a Radionuclide Calibrator

7.4.1 Initial Calibration

Commercially available radionuclide calibrators are initially calibrated by the manufacturers. The calibration is typically for common radionuclides in a specific geometry. The calibration provided may be traceable to national standards of radioactivity. Traceability can be established a number of ways and the uncertainty associated with the calibration factor will depend upon the calibration method used.[15] For initial calibrations ANSI[11] recommends that instruments be calibrated with standard sources of each radionuclide of interest, if available and that the geometry of the standard sources be identical to the geometry of the source to be assayed. This approach best meets the unbroken chain requirement of traceability (section 7.1).

Typically, however, the manufacturer determines the calibration settings from a limited range of traceable sources in a specific geometry on a master chamber or a typical production calibrator and generates a response-energy curve (section 4.3). The response-energy curve is

used to calculate calibration settings for additional radionuclides using simple interpolation or Monte Carlo calculations based on knowledge of their radioactive decay schemes. This methodology increases the uncertainty involved in the calibration by a significant amount. These calibration settings are then applied to each field instrument. Manufacturing differences between the master chamber and the field instrument will introduce uncertainties. In the calibration process, the manufacturers attempt to adjust for these uncertainties. The uncertainty associated with the calibration coefficients derived using the response-energy curve and published decay schemes ported to field instruments will be greater than for those determined by direct measurement standard sources and the definition of traceability may not be met.

Field instruments are calibrated using a limited number of standard sources. Typically a low-energy photon emitter (e.g., Co-57) and a high-energy photon emitter (e.g., Cs-137 or Co-60) in identical geometry are measured and the instrument adjusted to read accurately at two arbitrarily assigned calibration setting numbers.[11] Calibration settings for other radionuclides (previously calculated using the assigned calibration setting numbers and the detector response for the radionuclides) are then assumed to apply.[15] Other radionuclide standards may also be used to check instrument calibration (e.g., Tc-99m).

7.4.2 Subsidiary Calibration

Calibrations that are performed in addition to those provided by the manufacturer are referred to as subsidiary calibrations. Subsidiary calibrations should be performed to establish the response to radiopharmaceuticals in containers and/or volumes that are different from the containers and volumes used to calibrate the instrument. It is difficult to accurately model the response of a radionuclide calibrator for a radionuclide in a particular geometry and a much more dependable way to derive the calibration setting is to determine it empirically.[39] National or certified standards can be purchased and quantitatively transferred to the container geometries used for routine assays.

The procedures require some skill and should only be performed at facilities that have the necessary equipment and expertise. Specifically, performing syringe calibration in-house is very difficult.[18] A procedure for performing subsidiary calibrations is found in the Measurement Good Practice Guide No. 93[17] developed by the NPL and a list of necessary equipment in IAEA Technical Report Series No. 454.[1] Radiopharmaceutical suppliers that maintain their radionuclide calibrators as SSRC or as reference calibrators can provide medical facilities with traceable reference sources in routine geometries for subsidiary calibration and for establishing supplier equivalence (see section 10.3.2).

7.4.3 Recalibration

Radionuclide calibrator manufacturers recommend periodic recalibration. For example, one manufacturer recommends that periodic (every 4 or 5 years) manufacturer recalibration of the unit be performed to guarantee that the instrument's high reliability is maintained. When purchasing an instrument, the medical facility should be aware of such recommendations and the nature of the recalibration process offered by the manufacturer.

The ANSI standard[11] recommends calibration annually, following repair, and following extended periods of non-utilization. They recommend that calibrations be performed using standard sources of at least two radionuclides covering the energy and activity ranges of interest shall be performed. However, this appears to be a calibration check or accuracy test and not a calibration as defined above. Major repair could require the recalibration of all calibration settings, including replacement of the electrometer and/or the ionization chamber. For some calibrators the chamber and electrometer are matched and the electrometer is adjusted to compensate for differences between the field instruments and the master chamber or reference radionuclide calibrators for which the calibration settings were derived

8. Responsibility for Calibration and Traceability

8.1 Radionuclide Calibrator Manufacturer

The calibrator manufacturer should assure that all chambers pass stringent conformity tests against the master chamber or reference radionuclide calibrator to ensure the transferability of calibration coefficients. To do this, the calibrator manufacturer needs to build calibrators with known and controlled dimensional tolerances since calibration coefficients depend upon the physical characteristics of the specific ionization chamber.

Ideally, manufacturers should provide traceable calibrations for common source geometries and qualify when the calibrations may or may not be used for other geometries. However, at present, this is not the case and the user should be aware of the qualifications placed on the use of the calibrations provided by the manufacturers. For example, one radionuclide calibrator manufacturer provides calibrations based on syringe geometry (i.e., a "nominal 1-mm wall thickness") and includes the qualification that accurate measurement of unsealed sources in any other configuration must be with a new value. The manufacturer suggests an acceptable error of ±10%. Another manufacturer supplies calibration settings based upon the glass ampoules used by NIST and notes that they are a good approximation to an assay of a radiopharmaceutical in a plastic syringe but warns that the non-uniformity of the wall thickness of multi-injection dose vials may be a potential source of error. The manufacturer provides a table with estimates of the errors associated with syringe assays. The errors range from 2% to 15% for common clinically used radionuclides. For high-energy pure beta emitters (e.g., P-32 and Y-90), the manufacturer notes that the supplied calibration coefficients are for estimation only. More formal collaboration between radionuclide calibrator manufacturers and the NIST to generate calibration settings for common source geometries would help improve the accuracy of clinical assays.

8.2 Commercial Nuclear Pharmacy and Radiopharmaceutical Manufacturer

Commercial nuclear pharmacies and radiopharmaceutical manufacturers should calibrate their radionuclide calibrators using national or traceable standard sources for the geometries in which they supply their products. This is critical since the NRC allows licensees to accept approved-supplier's assays of unit dosages without further measurement. For a licensee that assays unit dosages supplied by commercial suppliers, the assays should be routinely compared

with those provided by the supplier and significant differences (see section 10.3.2, Supplier Equivalence) resolved.

8.3 Licensee

For direct measurement, a licensee is required to possess and use instrumentation (e.g., a radionuclide calibrator) to measure the activity of unsealed byproduct material before it is administered to each patient or human research subject and to calibrate the instrumentation in accordance with nationally recognized standards or the manufacturer's instructions and retain a record calibration.[2]

9. Pre-Purchase Considerations

9.1 Manufacturer's Declaration of Performance

As noted by the IAEA,[1] quality control of an instrument begins with its selection. In the United States, radionuclide calibrators are typically obtained from a limited number of calibrator manufacturers. These manufacturers are required to obtain an FDA (510K) approval for their calibrators.[50] However, the 510K requirements appear to be satisfied differently by different calibrator manufacturers and calibrator-operating characteristics (including calibration) may vary significantly. It is important that the user understand the operation and calibration of his calibrators before use.

This Task Group recommends that calibrator manufacturers provide the user with a declaration of performance that clearly states the accuracy of their calibration coefficients, how the coefficients were derived, and for what source geometry(ies) they may be applied. The manufacturer's declaration of performance should be available for a prospective buyer to review as a part of the selection process.

The declaration should include:

1. The traceability of calibration coefficients to national standards and the documented evidence of traceability.
2. Whether the calibration coefficients were obtained by direct measurement with a radioactivity standard source or calculated using a response-energy curve.
3. The expanded calibration uncertainty (at k=2 level) of the calibration coefficients for the source geometry (container and volume) and specific source position in the chamber used for calibration, including the uncertainty of the standard source.
4. The range of source positions in the chamber that can be used for assay within the declared uncertainty limits.
5. The ranges of activity that can be assayed within the declared uncertainty limits.
6. The applicability of calibration coefficients to the volumes and containers being used in practice and (if required) the availability of accurate correction factors and documentation of the additional uncertainties do they introduce.

7. For calibration coefficients obtained using a response-energy curve, the reference to the decay schemes used.
8. How the calibration coefficients are transported from the master or reference chamber to the production calibrator, including the process and the sources used.
9. The effect of manufacturer-supplied chamber shielding on the calibration coefficients.

9.2 Manufacturer's Recommended Quality Control Program

The FDA[50] requires a manufacturer to reference NRC requirements for routine calibration. As a result, several manufacturers' recommended quality control programs appear to be modified versions of dated NRC regulations and guidance. However, NRC regulations require licensees to calibrate the instrumentation in accordance with the manufacturer's instructions; thus, creating a circular reference. Licensees can also elect to follow a nationally recognized standard; however, no practical standard is available (at present).

The recommended quality programs from different manufacturers vary and although some variations are expected due to proprietary differences, the programs should be fundamentally the same. They should have at their core a set of performance tests and frequency of testing that reflect a current nationally recognized standard of practice. Tests in addition to the core tests that are recommended by the manufacturer for a specific model radionuclide calibrator should also be performed at the frequency suggested by the manufacturer. The manufacturer's recommended quality control program should be available for the prospective buyer to review as a part of the selection process. The manufacturer should be compliant with ISO 9000.[51]

10. Quality Assurance of Radionuclide Calibrators

10.1 Radionuclide Calibrator Installation, Operation, and Maintenance

For calibrator installation, operation, and maintenance, the manufacturer's operating manual shall be followed. Only authorized personnel shall operate the calibrator, and up-to-date instructions on the operation and maintenance of equipment shall be readily available for reference and use. Environmental requirements typically dictate that a radionuclide calibrator be placed on a solid, vibration-free base and operated at a relatively constant temperature and humidity (as recommended by the manufacturer). Direct sunlight, proximity to a room heater or air conditioner, and excessive humidity should also be avoided. In addition, the area should not be affected by high-activity sources. Additional shielding may be required for background reduction and/or personnel exposure reduction. Sterility requirements may also be a concern and the facility must aim at maintaining biological sterility and a dust-free environment.[1,11,17]

Radionuclide calibrators may be located within a primary engineering control (PEC) (e.g., laminar airflow workbenches or other similar clean air–producing device) to facilitate the compounding of sterile radiopharmaceutical preparations. All surfaces within the PEC, including those of the radionuclide calibrator, which are intimate to the aseptic processing area, require

frequent cleaning and disinfection. PEC surfaces are typically stainless steel and can thus easily withstand frequent cleaning and disinfection with a variety of agents. However, extreme caution must be employed to avoid damaging the radionuclide calibrator chamber and readout unit(s) when using cleaning and disinfection agents. Personnel should refer to the operation manual for guidance on proper safe cleaning. Typical cleaning instructions include warnings to avoid (1) getting water or liquids inside the chamber or readout enclosure, (2) use of aerosol dispensers to spray the equipment with cleaning and disinfection solutions or liquids, and (3) damaging the case or display screen by use of aromatic hydrocarbons, chlorinated solvents, or methanol-based cleaning solutions.

Generally, when the radionuclide calibrator chamber or readout unit(s) require cleaning, a sterile clean-room wipe cloth dampened with sterile water is best utilized. The surfaces of chamber plastic liners and plastic dippers are intimate to the aseptic processing area and thus must be cleaned and disinfected by appropriate means, such as a wiping with a sterile 70% isopropyl alcohol–dampened wipe cloth. Readout units may also be protected with plastic covers that can be disinfected frequently with sterile 70% isopropyl alcohol wipes.

10.2 Acceptance Testing

The IAEA[1] notes that the most critical step towards quality maintenance is carrying out acceptance tests independent of the manufacturer. They recommend that after installation acceptance tests be conducted to verify that the equipment conforms to the technical specifications certified by the manufacturer. In addition, they recommend that (ideally) a qualified expert define the technical specifications and carry out the acceptance testing of the equipment. The International Commission on Radiological Protection (ICRP)[5] defines acceptance test as a "test carried out at the request and with the participation of the user or his representative to ascertain by determination of proper performance parameters that the instrument meets the specifications claimed by the vendor" and recommends that an acceptance test be carried out at the time of installation and when appropriate after major service.

In addition to ascertaining that the radionuclide calibrator meets vendor specifications, test or reference data are obtained at acceptance testing and used for comparison with future routine tests.[1] The most thorough assessment of calibrator performance occurs at acceptance testing. Routine performance testing (see section 10.3) includes most of the same measurements. At acceptance testing or before first use, calibration settings for radionuclides in source geometries other than those provided by the calibrator manufacturers must be determined if the potential assay uncertainty is unacceptable (greater than 5%[1]). To do this for every syringe/vial size and volume is a daunting task but may only be required for a limited number of problem radionuclides (see section 5.3). Radiopharmaceutical manufacturers and commercial nuclear pharmacies should be required to provide dosages whose assays are accurate within ±5%. These dosages can be used to calibrate facility calibrators for the respective source geometries. At acceptance testing or before first use, those individuals who will use the radionuclide calibrator should be instructed in calibrator operation, maintenance, and quality control as appropriate. Instruction should include reading and comprehending the manufacturer's operating manual.

10.3 Routine Performance Tests

10.3.1 Routine Tests

Routine tests are repeated at specific intervals, to establish and document changes from the initial performance of the radionuclide calibrator established at acceptance testing. The overall objective of performance testing is to assure the continued accuracy of the dosage assays. The tests recommended in this document are based upon other published recommendations (mainly references 1, 11, 17, and 28) and are as follows:

- Physical Inspection
- System Electronics
- Clock Accuracy
- High Voltage
- Zero Adjust
- Background Response/Contamination Check
- Check Source (Constancy and Relative Response)
- Accuracy Test
- Reproducibility (Precision)
- System Linearity
- Supplier Equivalence

10.3.2 Test Descriptions

Physical Inspection
Check the calibrator and source holders for damage. Damaged source holders should be repaired or replaced. Check the display screen for proper operation and the console for keypad damage or damage to or malfunction of any pushbuttons/switches/dials. Check to assure that the chamber liner is in place and that small items (e.g., needle caps) have not fallen into the well.

System Electronics
Test the system electronics using the manufacturer-provided diagnostic testing (if applicable) and compare the results with the manufacturer's tolerances in accordance with the instructions in the operator's manual.

Clock Accuracy
For radionuclide calibrators that incorporate a clock, check the accuracy of the stored time. The time should be synchronized to a standard time (e.g., to values transmitted to cellular telephones or those maintained by NIST (www.time.gov). The time should be accurate to within 1 minute.[1] Accurate time measurements are essential when working with radionuclides that have short half-lives and/or for quantitative or semiquantitative imaging. The

clock will require updates to account for Daylight Savings Time (if observed). Clock accuracy should be checked following power outages or when investigating aberrant readings. Involved staff should be immediately informed of any clock adjustment to help minimize potential uncertainties in administered dosages. Other facility clocks referenced during dosage administration should be synchronized with the radionuclide calibrator clock. Calibrator clock adjustments should be performed in accordance with the instructions in the operator's manual.

High Voltage

Test the high voltage and compare the result with the manufacturer's tolerances in accordance with the instructions in the operator's manual.

Zero Adjust

The zero should be tested/adjusted each day-of-use prior to first use and compared with the manufacturer's tolerance in accordance with the instructions in the operator's manual.

Background Response/Contamination Check

Background may be caused by external radiation fields, chamber/dipper/liner contamination or by electronic noise. Most radionuclide calibrators are supplied with lead chamber shielding; however, for facilities that offer I-131 therapies and/or PET imaging, additional shielding may be required to further reduce external radiation to the chamber and/or exposure to the staff. Storage of inadequately shielded radioactive sources (e.g., Cs-137 or Co-60 radionuclide calibrator test sources, PET dosages or PET waste, or other high-energy photon emitters) in close proximity to the chamber may result in an unacceptably high background. For calibrators that have a background adjust function that automatically corrects for background, correction errors can result if the background changes between measurements.

The magnitude of the background should be established at acceptance testing and measured each day-of-use prior to first use and checked at each use. The measurement should be taken with no radioactive source in the chamber and on the most common radionuclide setting with the source holder and contamination shield in place. Any increase in the background above the normal value should be investigated. For calibrators that have a background adjust function, background should be within the allowed range of adjustment. Routine performance tests should be corrected for significant background contribution.

Check Source (Constancy and Relative Instrument Response)

Routinely measuring a long half-life check source (or standard source) allows the user to demonstrate the constancy of the calibrator's response (e.g., electrometer stability or gas pressure changes) over time. The measurements are taken (following the above daily tests) with a long half-life solid check source in the source holder in the measurement position. The measurements are compared to the initial measurements performed at acceptance testing and the results kept for the life of the chamber. The source should be measured on its own setting (e.g., Cs-137 on Cs-137 or Co-60 on Co-60). Using the same procedure, the source is also assayed on all commonly used settings (e.g., Cs-137 on Tc-99m, Cs-137 on I-131, Cs-137 on F-18, etc.). This is referred to a "relative response test"[1] and is a measure

of the constancy of the calibrator response for commonly used settings. If a standard source is used rather than a test source, the measurement obtained on the setting for the source radionuclide can also serve an accuracy test.

Measurements should be within ±5% of the decay-corrected initial values. For secondary standard radionuclide calibrators and reference radionuclide calibrators, measurements should be within ±2%. The measurements should be recorded and available for regulatory review.

Accuracy Test

Measurements are taken with the reference source in the source holder in the measurement position following the recommended daily tests. Source activity should be greater than 100 μCi (3.7×10^6 Bq).[11] In practice, accuracy testing involves testing with one or more traceable standards. The standards are typically in a solid plastic matrix in a vial format and include Co-57, Ba-133, Cs-137, and Co-60. The geometry of these standards is typically not identical to that of the standard sources used by the manufacturer to calibrate their systems (although at least one calibrator manufacturer calibrates their systems for these specific sources and source geometries in addition to their main calibration geometry).

This test is not a calibration; it is a test of system stability. Historically (in the United States), it involved measuring one to three traceable long-lived standards (typically, Co-57, Ba-133, and Cs-137) whose energies ranged over the linear portion of the response-energy curve. It was assumed that if the standards continued to measure accurately, the radionuclide calibrator was measuring correctly at all settings. Ideally, the test should use standards of radionuclides that are employed by the radionuclide calibrator manufacturer to set the system when transporting calibration settings to production models (e.g., Co-57 and Cs-137 or Co-57 and Co-60). Ascertaining, which radionuclides were used by the manufacturer should be part of the purchase process. The use of one source (e.g., Cs-137) in combination with the routine "relative response tests" should be sufficient for most medical facilities. For more complex programs, instrument stability should also be checked annually with at least two traceable reference sources and the radionuclides used should vary from year to year.[1,17]

Measurements of the long-lived standards and the two traceable reference sources should be within ±5% of the decay-corrected initial values. Secondary standard radionuclide calibrators and reference radionuclide calibrators should be within ±2%.[1,17] The measurements should be recorded and available for regulatory review.

Reproducibility (Precision)

Reproducibility is a measure of the percentage deviation of a series of measurements from the sample mean. For this test, a series of 10 consecutive measurements are obtained using a long-lived test source of greater than 100 μCi (3.7×10^6 Bq) with the test source in the source holder in the measurement position following the check source test.

Measurements should be within ±1% of the average measured activity for that source, assuming decay corrections over the measurement period are not required.[1,11,17] For secondary standard radionuclide calibrators and reference radionuclide calibrators, measurements should be within ±0.5%.[17] The measurements should be recorded and available for regulatory review.

System Linearity

As noted above (section 5.3), a calibrator is considered linear if the ratio of the measured response to the predicted response remains constant over the range of current inputs. The decaying source method, the shield method, and the graded source method[17] may be used to determine linearity. The graded source method involves manipulation and accurate measurement of stock solution aliquots and is not recommended for most facilities. The decaying source and shield method are addressed in the appendix. The decaying source method is recommended for secondary standard radionuclide calibrators and reference radionuclide calibrators. For field instruments, the decaying source method should be used at acceptance testing and following repair. The shield method should be sufficient for annual testing or the facility can perform the decaying source method.

Measurements are taken following the daily tests. The decaying source measurements are taken with the source in the source holder in the measurement position. The graded shielding measurements are taken per the shield manufacturer's instructions. At acceptance testing and following repair, measurements should be taken using the decaying source method from the highest activity (highest current) measured down to approximately 1 MBq. Annually, measurements should be taken between the maximum activity administered and 1 MBq over the range of use.

Measurements should be within ±5% of the expected values. For secondary standard radionuclide calibrators and reference radionuclide calibrators, linearity testing should be performed quarterly using the decaying source method and the measurements should be within ±2%.[1] For the shield method, the shields should be calibrated on a radionuclide calibrator whose linearity using the decaying source method is within ±5%. The measurements should be recorded and available for regulatory review.

Supplier Equivalence

It is recommended that medical facilities compare their assays to the assays (decay corrected) provided by the radiopharmaceutical suppliers. Equivalence should be determined at acceptance or first use and at least annually thereafter. For medical facilities that routinely order unit-dosages of short-lived radionuclides from local nuclear pharmacies, assay differences are often automatically assumed to be due to decay and are not investigated. However, differences may be due to other causes, including significant differences in calibration coefficients. Once equivalence has been established, facilities should compare assays (decay corrected) annually. Differences greater than ±10% should be investigated for cause. When initially establishing equivalence, assay differences should be less that ±5% and, if greater, the reason for the differences should be determined and corrected.

10.3.3 Manufacturer-Recommended Tests

Radionuclide calibrators should be operated in accordance with the manufacturer's instructions. If the manufacturer recommends tests in addition to those recommended above, they should be performed at the frequency recommended by the manufacturer. These additional tests are normally limited to tests of the electronic circuitry and other tests that are specific to their systems. As part of the purchase process, the manufacturer should be asked to document those routine tests that are in addition to the above-recommended tests.

10.4 Recommended Quality Control Programs

10.4.1 Test Frequencies

	Acceptance[a]	Daily[b]	Annually
Physical Inspection	X	X	X
System Electronic	X	X	X
Clock Accuracy	X	X	X
High Voltage	X	X	X
Zero Adjustment	X	X	X
Background	X	X	X
Check Source	X	X	X
Accuracy Test	X		X
Reproducibility	X		X
System Linearity	X		X
Supplier Equivalence	X		X

[a] And after repair.

[b] At the beginning of each day-of-use. **Note:** The term "day-of-use" may lead to some confusion for facilities that offer after-hour services. For purposes of radionuclide calibrator quality control, "day-of-use" means a normal 24-hour day starting at 12:00 a.m.

10.4.2 Commercial Nuclear Pharmacies (Including Manufacturers)

As noted above (section 2.3.1), the NRC allows dosage activity to be determined without measurement, based upon measurements provided by approved suppliers. This Task Group recommends that radiopharmaceutical manufacturers and nuclear pharmacies maintain their calibrators as secondary standard radionuclide calibrators or as reference calibrators with calibration settings for all source geometries that they dispense. Medical facilities could use reference standards provided by these suppliers to calibrate their radionuclide calibrators.

The user should be notified when dosages purchased from a local nuclear pharmacy have not been assayed by that pharmacy and are a "pass through" from the manufacturer. In that case, the local nuclear pharmacy may not have the correct calibration settings available on its radionuclide calibrator and the user may have to obtain calibration information from the radiopharmaceutical manufacturer.

10.5 Personnel Requirements

Facility management should establish (in writing) the qualifications and training requirements (including continuing education) necessary for those personnel who operate a radionuclide calibrator. Management should also identify (in writing) those specific individuals who are authorized to operate the calibrator as well as those individuals responsible for developing,

implementing, testing, and monitoring (including taking action to correct nonconformities) the radionuclide calibrator quality assurance program. Ideally, the quality assurance program should be the responsibility of a qualified medical physicist[52] or a qualified medical health physicist experienced in the use, calibration, and quality control of radionuclide calibrators.

10.6 Corrective Action

Any calibrator damage observed upon physical inspection that affects assay accuracy shall be repaired. Damaged source holders should be repaired or replaced. Holders from different manufacturers shall not be interchanged unless there is documentation that demonstrates equivalent assay accuracy. If the calibrator exhibits erratic performance, or the quality control tests fall outside of manufacturer's tolerances or acceptable percentage measurement limits, the instruments shall be recalibrated, or repaired and recalibrated as necessary.[11]

10.7 Documentation

Sufficient records need to be maintained to demonstrate proper calibrator operation, including, personnel training and competence testing, and adherence to the quality assurance program described in the section. The details of any calibrator maintenance or repair should also be recorded.

Acronyms and Abbreviations

AAPM	American Association of Physicists in Medicine
ANSI	American National Standards Institute
Bq	Becquerel
CFR	Code of Federal Regulations
Ci	Curie
DRL	Diagnostic Reference Level
EANM	European Association of Nuclear Medicine
fA	Femtoampere
FDA	Food and Drug Administration
FDG	Fluoro-2-deoxy-D-glucose
GBq	Gigabecquerel
HV	High Voltage
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IEC	International Electrotechnical Commission
IND	Investigational New Drug
keV	kiloelectronvolt
LNHB	Laboratoire National Henri Becquerel
mA	Microampere
MBq/g	Megabecquerel per gram
mCi	Millicurie
MeV	Megaelectronvolt
mL	Milliliter
mm	Millimeter

NCRP	National Council on Radiation Protection and Measurements
NIST	National Institute of Standards and Technology
NPL	National Physical Laboratory
NRC	Nuclear Regulatory Commission
pA/g	Picoampere per gram
PEC	Primary engineering control
PET	Positron Emission Tomography
PTB	Physikalisch – Technische Bundesanstalt
QA	Quality assurance
RDRC	Radioactive Drug Research Committee
RRC	Reference Radionuclide Calibrator
SRM	Standard References Materials
SSRC	Secondary Standard Radionuclide Calibrator
SUV	Standardized Uptake Value
USP-NF	United States Pharmacopeia - National Formulary

Appendix
Linearity Testing Protocols

Protocols for the decaying source method and the graded shield method are found in the IAEA Technical Report Series No. 454, Quality Assurance for Radioactivity Measurements in Nuclear Medicine.[1] A protocol for a decaying source method using Tc-99m is also found in the NPL Measurement Good Practice Guide No. 93, Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and their Quality Control.[15] Both documents are available on-line free of charge at http://www.npl.co.uk/publications (keyword "radionuclide calibrator") and http://www.iaea.org/Publications (under technical report series). Linearity testing programs are also incorporated into commercially available software for nuclear medicine and nuclear pharmacy management, quality control, and record keeping.

The following are supplementary recommendations:

1. For the Decaying Source Method and Facilities with Mo-99/Tc-99m Generators:

At acceptance testing and following repair:

Acquire a Tc-99m generator with an activity as large as will be used in the facility.

Elute the generator and assay the initial elution. Record the assay and the time of day at the start to the nearest minute

Assay the elution at least once every 2 hours (work-hours)—down to 1 MBq.

Record the time of day to the nearest minute—use the same clock.

For annual testing:

Use an activity as large as the largest patient dosage measured on the radionuclide calibrator.[†]

Assay the elution at least once every 2 hours (work-hours)—down to 1 MBq over the range of use (minimum 1 MBq).

Record the time of day to the nearest minute—use the same clock.

For unit dosages/bulk dosages:

At acceptance testing and following repair:

Assay an activity as large as the largest dosage measured on the radionuclide calibrator.[†]

[†] If I-131 therapy dosages are the largest patient dosages measured, use an activity of Tc-99m that is approximately 3 times the I-131 dosage.

Assay the elution at least once every 2 hours (work-hours)—down to 1 MBq.

Record the time of day to the nearest minute—use the same clock.

For annual testing:

Assay an activity as large as the largest patient dosage measured on the calibrator.

Assay the elution at least once every 2 hours (work-hours)—down to 1 MBq over the range of use.

Record the time of day to nearest minute—use the same clock.

2. For the Decaying Source Method and Facilities with F-18:

For unit dosage/bulk dosages:

At acceptance testing and following repair:

Assay an activity as large as the largest F-18 dosage measured on the calibrator.

Assay at least once every 30 minutes—down to 1 MBq.

Record the time of day at start to nearest 15 seconds—use the same clock.

For annual testing:

Use an activity as large as the largest patient dosage measured on the radionuclide calibrator.

Assay at least once every 30 minutes—down to 1 MBq over the range of use.

Record time of day at start to nearest 15 seconds—use the same clock.

3. For the Shield Method:

This Task Group recommends that the shield method be performed with Tc-99m using commercially available graded shields designed for Tc-99m. The shields must first be calibrated over the activity range of interest following the manufacturers protocol. The shields should be calibrated using a radionuclide calibrator that has demonstrated linearity within ±5% using the decay method. Measurements should be completed within 6 minutes to keep the error introduced by decay approximately 1%. If the shields are properly calibrated (and the calibration documented) for the specific photon energy of interest, the shield method may also be used with higher-energy photon emitters.

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Licensing of Radium-223 Dichloride

Ashley Cockerham
Medical Radiation Safety Team

September 20, 2012

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Overview

- History
- Issues
- Options
- Path Forward

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Previous Milestones: April 17, 2012

- Bayer provided an informational presentation to ACMUI
- ACMUI created a subcommittee to provide recommendations on licensing alpha emitters, including Ra-223, to NRC

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Previous Milestones: July 9, 2012

- ACMUI provided NRC a draft subcommittee report with recommendations for
  - Licensing Ra-223 under 10 CFR 35.300
  - Requiring an appropriate radioassay system for measurement of activity prior to and after administration using a NIST-traceable standard
- ACMUI to revise report to clarify drug status

Previous Milestones: July 16, 2012

- ACMUI provided final subcommittee report with substantive changes
  - Removal of wording "requiring" a radioassay system for direct measurement of activity before/after administration
  - Removal of statement that these recommendations apply to any future alpha particle-emitting radiopharmaceuticals
  - Removal of statement that Ra-223 dichloride "significantly prolongs survival"

5

Issue: Measurement of Activity

- Direct measurement of activity of unsealed byproduct material used under 10 CFR 35.300 is not required before or after administration
  - 10 CFR 35.63 applies
  - Direct measurement is one of three options in 35.63
- If ACMUI recommends this practice as a requirement for the medical use of Ra-223 dichloride, Ra-223 dichloride will need to be regulated under 10 CFR Part 35.1000

6

Options: Measurement of Activity

- Revise report to:
  - Recommend the medical use of Ra-223 dichloride under 10 CFR 35.300 without a requirement for direct measurement of activity before/after administration
  - Recommend the medical use of Ra-223 dichloride under 10 CFR 35.1000 with a requirement for direct measurement of activity before/after administration
  - Recommend a rulemaking change for requiring direct measurement of activity for all unsealed byproduct material for which a written directive is required

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Path Forward

- Clarify intent regarding direct measurement of activity before/after administration
- Acknowledge report changes regarding removal of statements about applicability for future alpha particle-emitting radiopharmaceuticals and prolonged survival
- Vote on final report
- Submit to NRC

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- CFR – Code of Federal Regulations
- Ra-223 – radium 223

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Radium-223 Dichloride Subcommittee Report

Pat Zanzonico, PhD
ACMUI

Subcommittee Membership

Darice Bailey
Susan Langhorst, Ph.D.
Steven Mattmuller
Christopher Palestro, M.D.
Orhan Suleiman, Ph.D.
Bruce Thomadsen, Ph.D.
James Welsh, M.D.
Pat Zanzonico, Ph.D. (Chair)

Subcommittee Charge

To provide recommendations on licensing of radium-223 (^{223}Ra) dichloride ($^{223}RaCl_2$)

Background

- **$^{223}RaCl_2$: A first-in-class, alpha particle-emitting therapeutic radiopharmaceutical**
- **Intended indication: Treatment of skeletal metastases in advanced, castrate-resistant prostate cancer**
- **Appears to be safe and effective and, uniquely, to prolong life**
- **Ready to inject: No preparation necessary nor radiochemical decomposition possible**
- **Patient-specific weight-normalized dosing (50 kBq/kg) from a pre-calibrated 1,000-kBq/ml solution**

1st Issue: Licensure

- Any special credentialing required to administer ^{223}RaCl?
- § 35.300 applies
- Credentialing options
  - § 35.390, Category (3) γ_s, β_s
  - § 35.390, Category (4) *Not "emissions-specific"*
  - § 35.390, New Category for α-emitters
  - § 35.1000, "Other" - specific license amendment

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Sub-Committee Recommendation

Physicians authorized to use therapeutic radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use $^{223}RaCl_2$ …

Licensing of authorized users of $^{223}RaCl_2$ under § 35.390 (Category (G)(3) or (G)(4)) or § 35.396(d)(2) is therefore recommended.

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2nd Issue: Calibration of Administered Activity

- End-user calibration
  - Is it necessary?
  - Can it be done accurately?
- Dose calibrators do not have ^{223}Ra setting
- ^{223}Ra
  - Secular equilibrium
  - Complex decay scheme
- NIST-traceable standard

7

Sub-Committee Recommendation

To minimize the probability of a therapeutic misadministration, an appropriate radioassay system for measurement of the ^{223}Ra activity prior to its administration and the residual activity following its administration is recommended

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Abbreviations and Acronyms

- **ACMUI:** Advisory Committee on Medical Uses of Isotopes
- **NIST:** National Institute of Standards and Technology
- **$^{223}RaCl_2$:** Radium-223 radium dichloride

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Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical UsesUses of Isotopes (ACMUI)
Subcommittee Report on Licensing for Radium-223 Chloride(^{223}Ra) Dichloride
July 16, 2012

Subcommittee Members
Darice Bailey, Susan Langhorst, Steven Mattmuller, Christopher Palestro, Orhan Suleiman, Bruce Thomadsen, James Welsh, and Pat Zanzonico (Chair)

Charge
To provide recommendations on licensing of radium-223 chloride (Ra-223 Cl)(^{223}Ra) dichloride ($^{223}RaCl_2$).

Summary Statement and Recommendations
Ra-223 Cl$^{223}RaCl_2$, currently a non-approved investigational agent undergoing clinical trials in the United States, represents a first-in-class, alpha particle-emitting therapeutic radiopharmaceutical. Based on relevant physical and biological considerations as well as clinicclinical data to date, it appears to be a safe, effective, and convenientits intended indication is treatment forof skeletal metastases in advanced, castrate-resistant prostate cancer, delivering high biologically effective doses to malignant cells in bone with relative sparing of hematopoietic marrow and other normal tissues. The injection volume for the body weight-adjusted dose of Ra-223 Cl ($^{223}RaCl_2$ (50 kBq/kg (1.35 □Ci/kg (50 kBq/kg)) is determined based on the vendor-supplied activity concentration in a pre-calibrated solution. Nonetheless, to minimize the probability of a therapeutic misadministration, requiring an appropriate radioassay system (ege.g., a dose calibrator) for measurement of the Ra-223^{223}Ra activity prior to its administration and the residual activity following its administration is recommended, as with any therapeutic radiopharmaceutical. This would require calibration of the radioassay system using, for example, a National Institute of Standards and Technology (NIST)-traceable Ra-223^{223}Ra standard. Ra-223 Cl$^{223}RaCl_2$ does not differ significantly in terms of clinical use and management, radiation safety, and logistics from currently approved radiopharmaceuticals. Therefore, physicians already authorized to use therapeutic radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use Ra-223 Cl$^{223}RaCl_2$. As such, licensing of authorized users of Ra-223 Cl$^{223}RaCl_2$ under § 35.390 (Category (G)(3) or (G)(4)), or § 35.396(d)(2), is therefore recommended. Importantly, the foregoing considerations, including licensing, are likely to apply to any future alpha particle-emitting radiopharmaceuticals generally.

Comment [a1]: Note removal of word "requiring"

Comment [a2]: Dr. Orhan Suleiman recommended removal of such a general statement, since the route of administration for $^{223}RaCl_2$ has a large impact on the committee's decision to recommend licensing in 300.

Clinical Background
Skeletal metastases commonly occur in many different malignancies, particularly advanced castrate-resistant prostate cancer, and are associated with severe morbidity and mortality (1). The resulting bone pain and possible fractures severely compromise the patient's quality of life and thus require effective treatment. Various non-radiotherapeutic modalities are available such as analgesics, hormone therapy, orchiectomy, cytostatic and cytotoxic drugs, bisphosphonates, and surgery but are not universally effective (2). External-beam radiotherapy is suitable only for well-defined localized bone metastases, and extended-field radiation for more generalized skeletal disease is often accompanied by excessive toxicity (3). In the setting of widely disseminated skeletal metastases, systemic, bone-targeting radionuclide therapies have emerged as a safe, convenient, and reasonably effective palliative and therapeutic modality (4, 5). Current

radiopharmaceuticals for palliation of painful skeletal metastases are exclusively beta particle emitters and include phosphorus-32 (~~P-32~~^{32}P) sodium phosphate, strontium-89 (~~Sr-89~~^{89}Sr) strontium chloride (Metastron™), yttrium-90 (~~Y-90~~^{90}Y) yttrium citrate, tin-117m (~~Sn-117m~~^{117m}Sn) diethylenetriamine pentaacetic acid (DTPA), samarium-153 (~~Sm-153~~^{153}Sm) lexidronam (Quadramet™), thulium-170 (~~Tm-170~~^{170}Tm) ethylene diamine tetramethylene phosphonate (EDTMP), lutecium-177 (~~Lu-177~~^{177}Lu) EDTMP, and rhenium-186 (~~Re-186~~^{186}Re) and rhenium-188 (~~Re-188~~^{188}Re) hydroxyethylidene diphosphonate (HEDP) (4,5). Currently approved radiopharmaceuticals for bone pain palliation include ~~P-32~~^{32}P sodium phosphate, ~~Sr-89~~^{89}Sr strontium chloride, and ~~Sm-153~~^{153}Sm lexidronam, while the others remain investigational.

~~Ra-223 Cl~~$^{223}RaCl_2$ (half-life: 11.43 days) is a calcium-mimetic alpha-particle emitter[1] which either avidly localizes in bone (particularly areas of active bone re-modeling typical of skeletal metastases)[2] or is rapidly excreted (6). ~~Ra-223~~^{223}Ra has only short-lived radioactive progeny, radon-219 (~~Rn-219~~^{219}Rn) (physical half-life: 3.96 seconds), polonium-215 (~~Po-215~~^{215}Po) (0.00178 second), ~~and~~ bismuth-211 (~~Bi-211~~^{211}Bi) (2.17 minutes), lead-211 (~~Pb-211~~^{211}Pb) (36.1 minutes) and thallium-207 (~~Tl-207~~^{207}Tl) (4.77 minutes) (6). The alpha emissions of ~~Ra-223~~^{223}Ra and its progeny are short-range, high-linear energy transfer (LET), and high-relative biological effectiveness (RBE) radiations and should deliver highly localized, highly cytocidal radiation to metastatic cells in bone with relative sparing of the near-by bone marrow (6). In addition, ~~Ra-223~~^{223}Ra and its progeny emit a number of externally countable and imageable x- and gamma-rays (81, 84, 154, and 269 keV) usable for pharmacokinetic studies, radiation dosimetry, and activity calibration (7). In principle, therefore, ~~Ra-223 Cl~~$^{223}RaCl_2$ potentially may provide more effective, less toxic palliation of skeletal metastases than current beta particle-emitting radiopharmaceuticals. Importantly, if approved by the US Food and Drug Administration (FDA), it would represent the very first alpha particle-emitting radiopharmaceutical in routine (i.e., non-investigational) clinical use.[3] in the United States.

~~Ra-223 Cl~~$^{223}RaCl_2$ has been extensively studied in patients, in Europe in particular as well as the United States (6, 8-13). Two open-label Phase-I trials (37 patients) and three double-blind Phase-II trials (255 patients) assessed radiation dosimetry, safety, and efficacy (decline in serum levels of prostate-specific antigen (PSA) and bone alkaline phosphatase (ALP) and prolongation of survival). Injected single doses varied from 5.2-252 kBq/kg (0.14-6.8 ☐Ci/kg) body mass. Repeated treatment regimens varied in number of doses and time-dose schedule. A Phase-II clinical trial in patients with symptomatic, hormone-refractory prostate cancer showed improvement in survival, PSA levels, and ALP levels compared with placebo (~~ie~~i.e., no treatment), with no differences in hematologic toxicity. An international double-blind, placebo-controlled randomized trial (ALpharadin in SYMptomatic Prostate CAncer [ALSYMPCA]) was subsequently undertaken to compare ~~Ra-223 Cl~~$^{223}RaCl_2$ with placebo in patients with symptomatic, androgen-independent prostate cancer with skeletal metastases. The study was stratified based on ALP levels at

[1] Other potential clinical alpha particle-emitting, bone-seeking agents include thorium-227 (~~Th-227~~^{227}Th) EDTMP, ~~Th-227~~^{227}Th tetraazacyclododecane tetra(methylene) phosphonic acid DOTMP (DOTMP), and ~~Bi-212~~^{212}Bi DOTMP (4,5) but these are not as advanced in terms of clinical use as ~~Alpharadin™~~ ^{223}Ra chloride.

[2] The propensity for internalized radium to localize in bone has long been recognized. For example, radium watch dial painters in the 1920s and 30s subsequently developed bone cancers and leukemias as a result of ingesting the radium-266 (~~Ra-226~~^{226}Ra)-containing paint when "twirling" their paint brush tips to a fine point in their mouths. Importantly, ~~Ra-226~~^{226}Ra has a much longer half-life, 1,600 years, than ~~Ra-223~~^{223}Ra, a critically important factor related to its carcinogenecity in bone.

[3] The FDA's revised policy on "Expanded Access to Investigational Drugs for Treatment Use" (21 CFR Parts 312 and 316, Federal Register Vol 74, No 155 August 13, 2009) allows the use of agents such as $^{223}RaCl_2$ to be expanded to a larger population beyond compassionate use in individual patients, but such "expanded-access" use would still require compliance with the Investigational New Drug (IND) record-keeping, safety, ethical, and other requirements associated with human-subject experimentation.

registration, bisphosphonate use, and prior treatment with docetaxel. A total of 922921 patients from 19 countries were enrolled, with overall survival being the primary endpoint. Importantly, the data demonstrated a statistically significant reduction in the risk of death for patients randomized to the Ra-223 $^{223}RaCl_2$ arm of the study (hazard ratio = 0.695; p = 0.00185), with a median overall survival of 14 months versus 11.2 months in the placebo arm. The overall survival benefit was seen across all sub-groups. The time to a skeletal-related event was also significantly longer for patients in the Ra-223 $^{223}RaCl_2$ versus placebo arm, 13.6 versus 8.4 months (p = 0.00046). The time to disease progression based on PSA and ALP levels was also significantly longer in the Ra-223 $^{223}RaCl_2$ arm. The patients randomized to Ra-223 $^{223}RaCl_2$ treatment tolerated it well. Both hematologic side-effects (grade-3 or -4 anemia, neutropenia, thrombocytopenia) and gastrointestinal side-effects (nausea, vomiting, diarrhea) did not occur with any greater frequency than with placebo. The former are related to localization of Ra-223 $^{223}RaCl_2$ in bone while the latter are related to its excretion through the intestines. It is noteworthy that the foregoing side-effects associated with therapeutic administration of Ra-223 Cl are $^{223}RaCl_2$are hardly unique. For example, the dose-limiting toxicity associated with iodine-131 (I-131 ^{131}I) iodide treatment of metastatic thyroid cancer and of radioimmunotherapy of cancer generally is most commonly myelosuppression. Nuclear Medicine physicians, Radiation Oncologists, and other physicians who administer radionuclide therapy are therefore already highly experienced in effectively managing such side-effects.

To summarize the clinical findings to date (6, 8-13), more than 1,000 prostate cancer patients have been treated with Ra-223 Cl $^{223}RaCl_2$ with single and repeated treatments with significant PSA declines and prolonged survival benefit, without therapy-limiting myelotoxicity, gastrointestinal toxicity or other significant normal-tissue toxicity compared to placebo. Although not yet approved by the FDA, Ra-223 Cl for routine clinical use, this investigational alpha particle-emitting agent appears to be the onlya promising bone-targeted radionuclide therapy which significantly prolongs survival. .

Comment [a3]: Because this drug is not approved, and this determination is pending with the FDA, Dr. Orhan Suleiman suggested deletion.

Radiation Safety and Logistical Considerations

Ra-223 Cl $^{223}RaCl_2$ and its progeny emit 95%, 4%, and 1% of their total radiation energy in the form of alpha particles, beta particles, and x- and gamma-rays, respectively (6). Alpha particles have very short ranges (of the order of 10□m in bone and soft tissue) and thus present no external, or direct, radiation hazard. As long as standard universal precautions[4] are observed and internalization is avoided, alpha particles pose no significant radiologic hazard overall - despite their high LET and high RBE. Importantly, this will likewise be the case for alpha particle-emitting radiopharmaceuticals in general. Universal precautions would also safeguard against the internal radiologic hazard of the small beta-particle component among the emissions of Ra-223 ^{223}Ra and its progeny. X- and gamma-rays are, of course, much more penetrating than alpha- and beta-particles but are emitted in very low abundance by Ra-223 ^{223}Ra and its progeny, with energies comparable to those of common diagnostic radionuclides such as a technetium-99m (Tc-99m ^{99m}Tc) (gamma-ray energy: 140 keV) and fluorine-18 (F-18 ^{18}F) (511 keV). At the same time, the single-dose administered activities of Ra-223 Cl, ~ $^{223}RaCl_2$, 50 kBq/kg (1.535 □Ci/kg) body mass or ~1003,500 kBq (95 □Ci) total for a 70-kg Standard Man, are several orders of magnitude lower than that of routine diagnostic radiopharmaceuticals (for which the administered activities are of the order of 370 MBq = 370,000 kBq (10 mCi = 10,000 □Ci)). Thus, for such low-abundance x- and gamma-rays and such low activities, the external, or direct, radiation exposure and shielding requirements for Ra-223 Cl $^{223}RaCl_2$ and its progeny are no greater than those for routinely used

[4] Universal precautions (ege.g., wearing of disposable gloves) constitute a method of infection control in which all human fluids, tissue etc are handled as if they are know to be infected with transmissible pathogens.

diagnostic radiopharmaceuticals - even though Ra-223 Cl $^{223}RaCl_2$ is a therapeutic agent (14). Further, patients do not require medical confinement following Ra-223 Cl $^{223}RaCl_2$ administration and may be treated on an outpatient basis. It should be reiterated, however, that Ra-223 Cl is still a non-approved (ie investigational) radiopharmaceutical.

As noted, Ra-223 ^{223}Ra has a physical half-life of 11.43 days; its radioactive progeny, Rn-219, Po-215, Bi-211, Pb-211 ^{219}Rn, ^{215}Po, ^{211}Bi, ^{211}Pb, and Tl-207 ^{207}Tl, have much shorter half-lives, ranging from 0.00178 second to 36.1 minutes. Ra-223 ^{223}Ra and its progeny thus have sufficiently short half-lives for on-site decay-in-storage of radioactively contaminated waste followed by disposal as non-radioactive waste. At the same time, the x- and gamma-rays emitted by Ra-223 ^{223}Ra and its progeny, although low in abundance, are sufficient for assay of any such waste. This can be done using conventional survey meters such as Geiger (G-M) counters - in order to verify that the exposure (or count) rates from contaminated or possibly contaminated waste are at or below background levels. Likewise, surveys of ambient exposure rates and of removable radioactive contamination (ieie.e., "wipes tests)") associated with the use of Ra-223 Cl $^{223}RaCl_2$ may be performed with instrumentation (surveys meters and well counters, respectively) already routinely available in Nuclear Medicine facilities.

Ra-223 Cl $^{223}RaCl_2$ is a simple salt of radium, and not a radiolabeled molecule. It therefore requires no synthesis or other preparation by the clinical site and does not undergo any sort of chemical decomposition. Quality control procedures for determination of radiochemical purity and special storage conditions (egee.g., refrigeration) are therefore not required for Ra-223 Cl $^{223}RaCl_2$. As distributed by Bayer Healthcare (Pittsburgh, PA), it is provided in a crimped glass vial as an injectable isotonic solution with an activity concentration of 1,000 kBq/ml (27 □Ci/ml) at calibration (15). The recommended administered activity is 50 kBq/kg (1.35 □Ci/kg–) body mass (15). A patient-specific volume of injectate, calculated using the following formula, is drawn directly from the vendor-provided Ra-223 Cl $^{223}RaCl_2$ solution (15):

$$\text{Volume to inject (ml)} = \frac{\text{Body mass (kg)} \times 50 \text{ kBq/kg}}{\text{Decay factor} \times 1000 \text{ kBq/ml}}$$

where the decay factor is the fractional decay factor (as derived from a vendor-provided "decay factor table," for example) for the time interval from the date and time of calibration of the Ra-223 Cl $^{223}RaCl_2$ to the planned date and time of administration.

Implicit in the foregoing dose-prescription algorithm is that the user is *not* required to assay the Ra-223 ^{223}Ra activity prior to its administration or the residual activity following its administration, as is typically done in Nuclear Medicine (especially for therapeutic administrations). Bayer Healthcare has asserted that measurement of the Ra-223 ^{223}Ra activities is *not* necessary, as the patient-specific dose corresponds to a calculated volume of the vendor-supplied solution with the vendor-specified pre-calibrated activity concentration (15). Bayer Healthcare has further asserted that such activity measurements would be potentially unreliable because (a) a setting for Ra-223 ^{223}Ra is not provided on currently available dose calibrators and (b) the pre-administration activity and, in particular, the residual activity would be too low (in the □tens of kBq (μ□Ci) range) to measure reliably (15). Ra-223 ^{223}Ra does, however, emit measurable x- and gamma-rays (7), and dose calibrators can thus be calibrated by the end user for Ra-223 ^{223}Ra using a National Institute of Standards and Technology (NIST)-traceable Ra-223 ^{223}Ra standard (16). In addition, assay of the pre-administration and residual Ra-223 ^{223}Ra activities, even if inexact, would help avoid potentially "catastrophic" misadministrations. By verifying that the actual pre-administration activity is consistent with the prescribed activity and that the residual activity is insignificant, clinically important over-dosing and/or under-dosing of the patient (egee.g., due to mis-calibration of the

vendor-supplied ~~Ra-223-Cl~~$^{223}RaCl_2$ solution or inaccurate drawing of the patient-specific injectate) as well as administration of an incorrect radionuclide could likely be avoided. Such activity assays would thus provide an additional level of safety at the treatment site independent of the vendor's manufacturing and calibration procedures. In a therapy setting, such redundancy, or cross-checking, is certainly prudent and is standard in Nuclear Medicine, especially in therapeutic applications. An appropriate radioassay system (~~e~~g., a dose calibrator) for measurement of the ~~Ra-223~~^{223}Ra activity prior to its administration or the residual activity following its administration is therefore recommended for the therapeutic use of ~~Ra-223-Cl~~$^{223}RaCl_2$.

Licensing Considerations

As noted, ~~Ra-223-Cl~~$^{223}RaCl_2$ represents a first-in-class - that is, an alpha particle-emitting - radiopharmaceutical. As such, it raises the issue of the appropriate NRC licensure for authorized users of this agent. ~~Ra-223-Cl~~$^{223}RaCl_2$ should be licensed under § 35.300 of the Code of Federal Regulations (CFR) (Appendix 1). Within the NRC's regulatory framework, there would appear to be several different licensing options for ~~Ra-223-Cl~~$^{223}RaCl_2$, namely, authorized users who meet training and experience requirements under § 35.390 (Appendix 2), § 35.396 (Appendix 3), or § 35.1000 A (Appendix 4). Despite its alpha-particle emissions, ~~Ra-223-Cl~~$^{223}RaCl_2$ does not differ fundamentally from current routinely used therapeutic radiopharmaceuticals. Given the similarities in clinical use and radiation safety considerations (as detailed above) between ~~Ra-223-Cl~~$^{223}RaCl_2$ and current therapeutic radiopharmaceuticals, the use of which is authorized under § 35.390 (Appendix 2), the use of ~~Ra-223-Cl~~$^{223}RaCl_2$ should likewise be authorized under § 35.390. It would appear that either Category (3) or (4) in § 35.390 would be appropriate for ~~Ra-223-Cl~~$^{223}RaCl_2$. Category (3) applies to, "Parenteral administration of any beta emitter, or a photon- emitting radionuclide with a photon energy less than 150 keV, for which a written directive is required"; it does not explicitly include or exclude alpha-particle emitters, however. Since ~~Ra-223~~^{223}Ra progeny emit beta particles as well as alpha particles, ~~Ra-223-Cl~~$^{223}RaCl_2$ technically might be considered a "Category (3)" radiopharmaceutical. However, even if "Category (3)" were interpreted as not applying to ~~Ra-223-Cl~~$^{223}RaCl_2$, Category (4), which applies to, "Parenteral administration of any other radionuclide, for which a written directive is required," would certainly apply. This same conclusion applies to§ 35.396 (Appendix 3). Licensing of ~~Ra-223-Cl~~$^{223}RaCl_2$ under § 35.1000 (Appendix 4) is not an appropriate option as that would imply it differs significantly in terms of clinical use and management, radiation safety, and logistics from current therapeutic radiopharmaceuticals, and this is not the case. Physicians already authorized to use such radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use ~~Ra-223-Cl~~$^{223}RaCl_2$, and should not be required to provide additional training-and-experience documentation to be licensed for its use.

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Appendix 1

§ 35.300 Use of unsealed byproduct material for which a written directive is required.

A licensee may use any unsealed byproduct material prepared for medical use and for which a written directive is required that is-

(a) Obtained from:

(1) A manufacturer or preparer licensed under § 32.72 of this chapter or equivalent Agreement State requirements; or

(2) A PET radioactive drug producer licensed under § 30.32(j) of this chapter or equivalent Agreement State requirements; or

(b) Excluding production of PET radionuclides, prepared by:

(1) An authorized nuclear pharmacist;

(2) A physician who is an authorized user and who meets the requirements specified in §§ 35.290, 35.390, or

(3) An individual under the supervision, as specified in § 35.27, of the authorized nuclear pharmacist in paragraph (b)(1) of this section or the physician who is an authorized user in paragraph (b)(2) of this section; or

(c) Obtained from and prepared by an NRC or Agreement State licensee for use in research in accordance with an Investigational New Drug (IND) protocol accepted by FDA; or

(d) Prepared by the licensee for use in research in accordance with an Investigational New Drug (IND) protocol accepted by FDA.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19324, Apr. 21, 2003; 69 FR 55738, Sep. 16, 2004; 71 FR 15009, Mar. 27, 2006; 72 FR 55932 Oct. 1, 2007]

Appendix 2

§ 35.390 Training for use of unsealed byproduct material for which a written directive is required.

Except as provided in § 35.57, the licensee shall require an authorized user of unsealed byproduct material for the uses authorized under § 35.300 to be a physician who-

(a) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State and who meets the requirements in paragraphs (b)(1)(ii)(G) and (b)(2) of this section. (Specialty boards whose certification processes have been recognized by the Commission or an Agreement State will be posted on the NRC's Web page.) To be recognized, a specialty board shall require all candidates for certification to:

(1) Successfully complete residency training in a radiation therapy or nuclear medicine training program or a program in a related medical specialty. These residency training programs must include 700 hours of training and experience as described in paragraphs (b)(1)(i) through (b)(1)(ii)(E) of this section. Eligible training programs must be approved by the Residency Review Committee of the Accreditation Council for Graduate Medical Education, the Royal College of Physicians and Surgeons of Canada, or the Committee on Post-Graduate Training of the American Osteopathic Association; and

(2) Pass an examination, administered by diplomates of the specialty board, which tests knowledge and competence in radiation safety, radionuclide handling, quality assurance, and clinical use of unsealed byproduct material for which a written directive is required; or

(b)(1) Has completed 700 hours of training and experience, including a minimum of 200 hours of classroom and laboratory training, in basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material requiring a written directive. The training and experience must include-

(i) Classroom and laboratory training in the following areas-

(A) Radiation physics and instrumentation;

(B) Radiation protection;

(C) Mathematics pertaining to the use and measurement of radioactivity;

(D) Chemistry of byproduct material for medical use; and

(E) Radiation biology; and

(ii) Work experience, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, or equivalent Agreement State requirements. A supervising authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as the individual requesting authorized user status. The work experience must involve-

(A) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys;

(B) Performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for proper operation of survey meters;

(C) Calculating, measuring, and safely preparing patient or human research subject dosages;

(D) Using administrative controls to prevent a medical event involving the use of unsealed byproduct material;

(E) Using procedures to contain spilled byproduct material safely and using proper decontamination procedures;

(F) [Reserved]

(G) Administering dosages of radioactive drugs to patients or human research subjects involving a minimum of three cases in each of the following categories for which the individual is requesting authorized user status-

(*1*) Oral administration of less than or equal to 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131, for which a written directive is required;

(*2*) Oral administration of greater than 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131[2];

(*3*) Parenteral administration of any beta emitter, or a photon- emitting radionuclide with a photon energy less than 150 keV, for which a written directive is required; and/or

(*4*) Parenteral administration of any other radionuclide, for which a written directive is required; and

(2) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraphs (a)(1) and (b)(1)(ii)(G) or (b)(1) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for the medical uses authorized under § 35.300. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, or equivalent Agreement State requirements. The preceptor authorized user, who meets the requirements in § 35.390(b) must have experience in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as the individual requesting authorized user status.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19325, Apr. 21, 2003; 68 FR 75389, Dec. 31, 2003; 69 FR 55738, Sep. 16, 2004; 70 FR 16364, Mar. 30, 2005; 71 FR 15009, Mar. 27, 2006; 74 FR 33905, Jul. 14, 2009]

[2] Experience with at least 3 cases in Category (G)(*2*) also satisfies the requirement in Category (G)(*1*)

Appendix 3

§ 35.396 Training for the parenteral administration of unsealed byproduct material requiring a written directive.

Except as provided in § 35.57, the licensee shall require an authorized user for the parenteral administration requiring a written directive, to be a physician who-

(a) Is an authorized user under § 35.390 for uses listed in §§ 35.390(b)(1)(ii)(G)(3) or 35.390(b)(1)(ii)(G)(4), or equivalent Agreement State requirements; or

(b) Is an authorized user under §§ 35.490, 35.690, or equivalent Agreement State requirements and who meets the requirements in paragraph (d) of this section; or

(c) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State under §§ 35.490 or 35.690, and who meets the requirements in paragraph (d) of this section.

(d)(1) Has successfully completed 80 hours of classroom and laboratory training, applicable to parenteral administrations, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other radionuclide for which a written directive is required. The training must include—

(i) Radiation physics and instrumentation;

(ii) Radiation protection;

(iii) Mathematics pertaining to the use and measurement of radioactivity;

(iv) Chemistry of byproduct material for medical use; and

(v) Radiation biology; and

(2) Has work experience, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements, in the parenteral administration, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other radionuclide for which a written directive is required. A supervising authorized user who meets the requirements in § 35.390 must have experience in administering dosages as specified in §§ 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(4). The work experience must involve—

(i) Ordering, receiving, and unpacking radioactive materials safely, and performing the related radiation surveys;

(ii) Performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for proper operation of survey meters;

(iii) Calculating, measuring, and safely preparing patient or human research subject dosages;

(iv) Using administrative controls to prevent a medical event involving the use of unsealed byproduct material;

(v) Using procedures to contain spilled byproduct material safely, and using proper decontamination procedures; and

(vi) Administering dosages to patients or human research subjects, that include at least 3 cases involving the parenteral administration, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV and/or at least 3 cases involving the parenteral administration of any other radionuclide, for which a written directive is required; and

(3) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraph (b) or (c) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for the parenteral administration of unsealed byproduct material requiring a written directive. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements. A preceptor authorized user, who meets the requirements in § 35.390, must have experience in administering dosages as specified in §§ 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(*4*).

[70 FR 16365, Mar. 30, 2005; 71 FR 15010. Mar. 27, 2006; 74 FR 33906, Jul. 14, 2009]

Appendix 4

§ 35.1000 Other medical uses of byproduct material or radiation from byproduct material.

A licensee may use byproduct material or a radiation source approved for medical use which is not specifically addressed in subparts D through H of this part if--

(a) The applicant or licensee has submitted the information required by § 35.12(b) through (d); and

(b) The applicant or licensee has received written approval from the Commission in a license or license amendment and uses the material in accordance with the regulations and specific conditions the Commission considers necessary for the medical use of the material.

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Status on Data Collection on Patient Release

Michael Fuller
Team Leader
Medical Radiation Safety Team

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Purpose

- To provide an overview and an update of NRC initiatives related to the release of patients administered I-131, especially those who do not immediately return to their primary residences.

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Background: Release Regulations

- May 1997 - NRC revised the patient release regulation (10 CFR 35.75) to release the patient based on the dose to the maximally exposed individual.
- Patients can be released if: The dose to any other individual from exposure to the released patient is not likely to exceed 5 mSv (0.5 rem).

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Background: Release Regulations

- The regulations require that written instructions on how to keep doses to other individuals as low as reasonably achievable (ALARA) be given to patients if there is a possibility that doses to any other individual would exceed 1 mSv (0.1 rem).
- The licensee is required to maintain a record of the basis for authorizing the release.

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Iodine-131 Administration

- Increased activities
  - Increased number of procedures
  - Wide variability of administered activities
- Unique Characteristics
  - Volatility
  - Increased potential for external/internal radiation doses
  - Contamination
- Emissions

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Current Guidance

- Regulatory Guide 8.39: Release of Patients Administered Radioactive Materials
- NUREG-1556 Vol. 9: Consolidated Guidance about Materials Licenses: Program-Specific Guidance About Medical Licenses
- NRC RIS: 2008-07 Dose Limit For Patient Release Under 10 CFR 35.75

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Current Guidance

- NRC RIS: 2008-11 Precautions To Protect Children Who May Come In Contact With Patients Released After Therapeutic Administration Of Iodine-131
- NRC RIS: 2011-01 NRC Policy On Release Of Iodine-131 Therapy Patients Under 10 CFR 35.75 To Locations Other Than Private Residences

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Recent Initiatives

- Commission directed NRC Staff to:
  - Evaluate whether there are gaps in the available empirical data on doses received by members of the public from release of patients treated with medical isotopes.
  - Determine how the agency could go about collecting additional data, if needed.
  - Assess the feasibility of revisiting the dose assessment used to support the 1997 patient release rulemaking.

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Data Collection Regarding Patient Release

- In March 2012, the Commission directed staff to perform analytical and limited empirical research/data collection, and revisit calculations and methods described in the Regulatory Guide 8.39 for patient release.

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Staff's Proposed Research

- Literature Review
- Review assumptions used in Reg. Guide 8.39
- Survey habits of Released Patients
- Perform empirical measurements
- Assess internal and external radiation exposure
- Re-assess the adequacy of Regulatory Guide 8.39

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Conclusions

- Depending on the outcome of the research NRC may:
  - Update Regulatory Guide 8.39
  - Take other actions, as appropriate.

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QUESTIONS?

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Part 35 Rulemakings Update

Neelam Bhalla and Ed Lohr
Rulemaking Branch B
Division of Intergovernmental Liaison and Rulemaking
Office of Federal and State Materials and Environmental Management Programs

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Part 35 Rulemakings

There are 2 proposed medical rulemakings:

1. The Expanded Rulemaking
2. The Medical Event Rulemaking

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Combining Rulemakings: Commission Direction

- In a Staff Requirement Memorandum to the Permanent Implant Brachytherapy paper, SECY-12-0053, the Commission has directed the staff to:
- 1. Include the Medical Event Rulemaking into the Expanded Rulemaking, and

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Combining Rulemakings: Commission Direction (contd.)

2. Provide the Commission with a new paper at any time a substantive delay in the completion schedule for this rule becomes apparent. The paper should explain the schedule delay and the impact of separating the Medical Event rule from the combined rulemaking.

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Current Schedule of Combined Rulemaking

Proposed Rule to Commission:
Mid- 2013
Final Rule to Commission:
Late- 2014

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Tentative Dates For ACMUI Review

We would be requesting the Advisory Committee on the Medical Uses of Isotopes (ACMUI) to review the draft *Federal Register* Notice (FRN) before it goes to the Commission

- Draft FRN to ACMUI December 2012
- Review period 90 days
- ACMUI comments March 2013

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Questions and Comments

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Update, Proposed Regulatory Changes– Permanent Implant Brachytherapy

Ronald Zelac, Ph.D.

ACMUI Meeting

September 20, 2012

Main Objectives of Recommendations

- Change treatment site medical event (ME) criterion from dose-based to source-strength-based.
- Remove ambiguity from written directive (WD) and ME requirements.

Basis For Current Recommendations

- ACMUI revised final report.
- Stakeholder input from workshops and public meetings.
- ASTRO recommendations.
- OAS recommendations.

Status of Recommendations

- SECY-12-0053, "Recommendations on Regulatory Changes for Permanent Implant Brachytherapy Programs" (4/5/12)
- SRM-SECY-12-0053, "Staff Requirements…" (8/13/12)

Recommendations, 10 CFR 35.3045, Reporting MEs

- Define separate ME criteria for permanent implant brachytherapy utilizing radioactive sources.
- Treatment site ME if 20% or more of implanted sources are outside the intended implant location.

5

Recommendations, 10 CFR 35.3045 (cont.)

- For normal tissue in neighboring structures – ME if dose to contiguous ≥5 cc exceeds 150% of the absorbed dose prescribed for the treatment site.

6

Recommendations, 10 CFR 35.3045 (cont.)

- For normal tissue structures within treatment site – ME if dose to contiguous ≥5 cc exceeds 150% of the expected absorbed dose for that tissue.

7

Recommendations, 10 CFR 35.3045 (cont.)

- ME if treatment is administered:
  - using wrong radionuclide;
  - using wrong source strength (+/- 20%) as specified in the WD;
  - with delivery to the wrong patient;

8

Recommendations, 10 CFR 35.3045 (cont.)

- ME if treatment is administered:
  - with implantation directly into the wrong site or body part;
  - with delivery using the wrong modality;
  - using leaking sources.

9

Recommendations, 10 CFR 35.3045 (cont.)

- All of the proposed ME criteria reflect circumstances in which there is actual or potential harm to patients being treated.

10

Recommendations, 10 CFR 35.40, WDs

- Define separate criteria for permanent implant brachytherapy
- Delete "total dose" as an option for completing the WD
- Replace "before completion of the procedure"

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Staff position re: these current recommendations

- Patient interests would be protected.
- Physicians would be able to take medically necessary actions.

12

Staff position re: these current recommendations (cont.)

- **NRC would be able to continue detecting failures in process, procedures, and training plus misapplications by AUs.**
- **Stakeholder input is reflected in these recommendations.**

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- ASTRO – American Society for Radiation Oncology
- AU – Authorized User
- cc – cubic centimeter
- ME – Medical Event
- OAS – Organization of Agreement States
- WD – Written Directive

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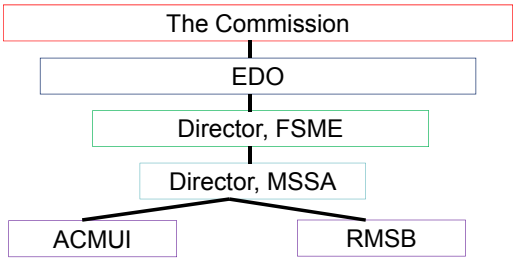
ACMUI Reporting Structure

Sophie Holiday
Medical Radiation Safety Team
Office of Federal and State Materials and Environmental Management Programs

Outline

- Current Reporting Structure
- Annual Review
- SRM-SECY-11-0049
- September 22, 2011 Meeting
- Discussion

Current Reporting Structure



Current Reporting Structure

July 21, 2010 – SRM

January 5, 2011 Teleconference

- Recommendation to maintain current reporting structure with increased staff support

Annual Review

Jan 12, 2011 Teleconference

- **Recommendation by ACMUI to have an annual review of reporting structure**

5

SECY-11-0049

- **SRM M100708B directed staff to provide feedback on the pros/cons for restructuring ACMUI to report to the Commission.**
- **Included both ACMUI and staff recommendations**
- **Proposed maintaining current reporting structure or reporting through ACRS.**

6

SRM-SECY-11-0049

- **Approved the current reporting structure**
- **Acknowledged ACMUI's intent to review structure annually**
- **Directed a consideration of an increase of resources for FY2013 budget proposal**
- **Directed a consult with ACRS**

7

September 22, 2011 Meeting

- **Outlined the differences between ACMUI and ACRS Reporting**
- **Request for additional staffing resources?**

8

Acronyms

- ACRS – Advisory Committee on Reactor Safeguards
- EDO – Executive Director for Operations
- FSME – Office of Federal and State Materials and Environmental Management Programs
- FY – Fiscal Year

9

Acronyms

- MSSA – Division of Materials Safety and State Agreements
- RMSB – Radioactive Materials Safety Branch
- SECY – Office of the Secretary
- SRM – Staff Requirements Memorandum

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Discussion

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MEDICAL ABNORMAL OCCURRENCE (AO) CRITERIA

Suggested Refinement to Proposed Criteria

Angela R. McIntosh
Abnormal Occurrences Coordinator
Office of Federal and State Materials
and Environmental Management Programs

CURRENT ACMUI RECOMMENED MEDICAL AO CRITERIA

For Medical Licensees

- A medical event that results in death; or
- A significant impact on patient health that would result in permanent functional damage or a significant adverse health effect that would not have been expected from the normal treatment regimen, as determined by an NRC or Agreement State – designated consultant physician(s).

2

NRC PROPOSED REFINEMENT

Events Involving Patients or Human Research Subjects [17]

- A medical event that results in a dose other than the dose to the intended target that is:
  - Greater than or equal to 1 Gy (100 rad) to a major portion of the bone marrow or to the lens of the eye; **or**
  - Greater than or equal to 2.5 Gy (250 rad) to the gonads; **or**
  - Greater than or equal to 10 Gy (1,000 rad to any other unintended organ or tissues other than the treatment site; **and**

[17] Criteria III.A.3 and III.A.4 also apply.

3

NRC PROPOSED REFINEMENT

- Results in a significant impact on patient health that would result in **one or more** of the following, as determined by a consultant physician(s) deemed qualified by NRC or an Agreement State:
  - Unintended permanent functional damage to an organ.
  - Unintended permanent functional damage to a physiological system.
  - A significant unexpected adverse health effect.
  - Death.

4

NRC PROPOSED REFINEMENT

~~For Medical Licensees~~ Events Involving Patients or Human Research Subjects [17]

- A medical event that results in ~~death~~ a dose other than the dose to the intended target that is:
  - Greater than or equal to 1 Gy (100 rad) to a major portion of the bone marrow or to the lens of the eye; **or**
  - Greater than or equal to 2.5 Gy (250 rad) to the gonads; **or**
  - Greater than or equal to 10 Gy (1,000 rad to any other unintended organ or tissues other than the treatment site; **and**

Note: Blue font is indicative of language currently used to capture Medical AOs. NRC staff recommends retention of this language.

5

NRC PROPOSED REFINEMENT

- Results in a significant impact on patient health that would result in ~~permanent functional damage or a significant adverse health effect that would have not been expected from the normal treatment regimen, as determined by an NRC or Agreement State designated consultant physician(s)~~ **one or more** of the following, as determined by a consultant physician(s) deemed qualified by NRC or an Agreement State:
  - Unintended permanent functional damage to an organ.
  - Unintended permanent functional damage to a physiological system.
  - A significant unexpected adverse health effect.
  - Death.

6

NRC PROPOSED REFINEMENT
(Footnote 17 Reference)

III. Events at Facilities Other than Nuclear Power Plants and All Transportation Events

A. Events Involving Design, Analysis, Construction, Testing Operation, Transport, Use, or Disposal of Licensed Facilities or Regulated Materials

1. An accident criticality.
2. A major deficiency in design, construction…
3. **A serious safety-significant deficiency in management or procedural controls.**

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NRC PROPOSED REFINEMENT

III. Events at Facilities Other than Nuclear Power Plants and All Transportation Events **(continued)**

4. **A series of events (in which the individual events in which individual events are not of major importance), recurring incidents, or incidents with implications for similar facilities (generic incidents that raise a major safety concern.**

8

SUMMARY OF REFINEMENTS

- **Dose Criteria Retained**
  - "*Greater than or equal to 1 Gy (100 rad)…*"
  - Useful to staff for the non-arbitrary, consistent identification of events that could be serious.
  - Aids in efficient use of NRC staff resources.
- **Clarification:**
  - Minimally only one of the second set of criteria need be met.
  - "…**one or more** of the following, as determined by a consultant physician(s)…"

9

SUMMARY OF REFINEMENTS

- **Proposal to Apply Generic Trend Criteria to Medical Facilities**
  - "*Serious safety-significant deficiency in management or procedural controls.*"
  - "*A series of events (in which the individual events are not of major importance), recurring incidents, or incidents with implications for similar facilities (generic incidents) that raise a major safety concern.*"

10

NEXT STEPS

- Agreement State Early Comment
- Commission Review
- Publication in *Federal Register* (90 days)
- Staff Incorporation of Comments
- Commission Review/Final Approval
- Final AO Criteria in *Federal Register*

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DISCUSSION

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U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Reducing Occupational Dose Limits

SECY-12-0064

Recommendations for Policy and Technical Direction to Revise Radiation Protection Regulations and Guidance

Advisory Committee on the Medical Uses of Isotopes
September 21, 2012

Donald A. Cool, Ph.D.
Senior Advisor Radiation Safety and International Liaison

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Background

- NRC regulations based on national and international recommendations
  - NCRP, BEIR
  - ICRP, UNSCEAR
- 10 CFR Part 20 last major revision in 1991, based in ICRP Publication 26 from 1977
- Other portions of regulations still based on ICRP Publications 1 and 2, 1959 and 1960

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Background

- ICRP revised recommendations announced in December, 2007
- NRC staff analysis indicated areas warranting consideration for revisions – SECY-08-0197, December, 2008
- Commission approved staff recommendation to engage stakeholders and initiate development of technical basis materials on April 2, 2009
- Staff Recommendations – SECY-12-0064, April 25, 2012

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Protecting People and the Environment

Outreach Activities

- Phase I of outreach included:
  - Presentations to numerous organizations and groups
  - FRN published inviting inputs (72 FR 32198)
- Phase II Workshops
  - FRN published with issues and questions (75 FR 59160)
  - Workshops in Washington, Los Angeles, and Houston
  - Comments accepted through January 31, 2011

Outreach Activities

- Phase III
  - FRN published for lens of the eye (76 FR 53847)
  - FRN closed October 31, 2011

5

Stakeholder Dialogue

- Total of 59 comments docketed
- General support for changes to reflect current dose calculation methodology and terminology
- Opposition to changes to dose limits and ALARA provisions
  - View that risk did not warrant changes
  - View that impacts would be unacceptable
  - View that sources and uses in US are different, and justify different limits

6

Radiation Risk

- Current basis supporting NRC regulations is a mixture of risk information ranging from 1958 to 1990
- 10 CFR Part 20 based on assumed risk of 1.25×10^{-4} per rem cancer mortality and risk of heritable disease

7

Radiation Risk

- Current radiation risk $\approx 5 \times 10^{-4}$ per rem
  - Considered mortality, morbidity and hereditary effects
  - Comparable results from UNSCEAR, ICRP, BEIR, NCRP
  - EPA “Blue Book” values even higher
- LNT for practical purposes of radiation protection

8

Methodology Basis

- 10 CFR Part 50, Appendix I based on ICRP 1 and 2 MPC critical organ approach
- 10 CFR Part 20
  - Generally based on ICRP 26 and 30 TEDE approach
  - Public Exposure aligned to newer recommendations and increased risk in final rule
  - Occupational Exposure not aligned in final rule

9

Methodology Basis

- Licensees granted use of ICRP 60+ approach on case by case basis for internal dosimetry
- Effective dose recognized for external exposure

10

Basis for Occupational Limits

- 1977
  - average annual risk of accidental death in industries generally accepted as safe working environment – 1×10^{-4}
  - 5 rem value based on expectation that most individuals would be unlikely to exceed 1 rem

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Basis for Occupational Limits

- 1990
  - Multi-attribute approach
  - Objective to prevent cumulative exposure to less than 100 rem
  - Average and maximum values to provide flexibility for implementation

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Update Dose Assessment Methods

- General support for moving to consistently incorporate latest scientific information and modeling.
- Stakeholders supported delaying rulemaking until ICRP completes work on dose coefficients
- Staff Recommendation:
  - Adopt updated methodologies and models
  - Continue with Appendix B in rule for ALI and DAC
  - Use updated methods for 10 CFR Part 50, Appendix I, and other portions of the regulations to establish new consistent basis

Revise Terminology

- Changes in methodology resulted in changes in Terminology in 1990
- Stakeholders supported changes, but noted impacts in updating procedures, records, reports, and training
- Staff Recommendation:
  - Develop Regulatory Basis to incorporate updated terminology.
  - Explore options to provide flexibility during implementation

Occupational TEDE Limit

- Conclusions
  - Limit does not reflect current risk basis
  - Exposures near limit could exceed recommended cumulative total
  - 99.7% of individuals were below 2 rem in 2010
  - Flexibility needed – but only for some licensees and small groups of individuals
  - Differences between U.S. and other countries present complications to trans-boundary movement of workers

Occupational Exposure Distribution

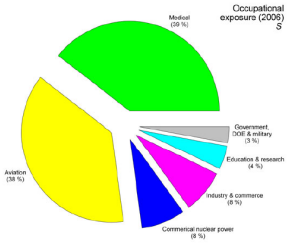

Fig. 7.3. Percent contribution of various sources to S for occupational exposure (1,400 person-Sv) for 2006. Percent values have been rounded to the nearest 1 % [see Table 7.3 for the values of S (person-sievert)].

Medical Occupational Exposure

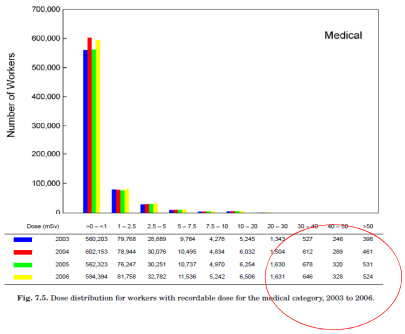

Fig. 7.5. Dose distribution for workers with recordable dose for the medical category, 2003 to 2006.

Dose (mSv)	>0 – <1	1 – 2.5	2.5 – 5	5 – 7.5	7.5 – 10	10 – 20	20 – 30	30 – 40	40 – 50	>50
2003	560,203	79,768	28,889	9,764	4,276	5,245	1,342	527	246	398
2004	602,153	78,944	30,076	10,495	4,834	6,032	1,504	612	289	461
2005	562,323	76,247	30,251	10,737	4,970	6,254	1,630	676	320	531
2006	594,384	81,758	32,782	11,536	5,242	6,506	1,631	646	328	524

Occupational TEDE Limit

- Stakeholder Feedback:
  - Little support for change to regulation
  - Suggestions of significant impact on licensed activities and delivery of health care
  - Suggestions that there could be an increase in the rate of non-compliance
  - Statements that sources and uses in U.S. are basis for having different dose limits

Occupational TEDE Limit

- Staff Recommendation:
  - Develop regulatory basis for reducing limit to 2 rem (20 mSv/yr)
  - Explore mechanism for flexibility for those licensees who need it through specified approval process

Lens of the Eye

- ICRP recommendation issued April, 2011
  - Reduced limit based on evidence that radiation induces cataracts at lower cumulative levels than previously estimated (≈ 50 rem (500 mSv)).
  - TEDE and LDE similar in many situations except
    - Shielding of body
    - Lower energy β/γ
  - Already incorporated into IAEA Basic Safety Standard
    - IAEA Technical Meeting to develop initial implementation guidance, October 2 – 4, 2012

Lens of the Eye

- Mixed Stakeholder Feedback:
  - Scientific information questioned
  - Concern about numeric LDE value less than TEDE
  - Concern about type of effect
  - Significant impacts in interventional radiology and cardiology

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Lens of the Eye

- Staff Recommendation:
  - Develop regulatory basis for reducing limit
  - Consider single values of 5 rem (50 mSv) or 2 rem (20 mSv)
  - Continue dialogue on how prevention of cataracts should be viewed in comparison with the potential induction of cancer

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Embryo/Fetus

- ICRP recommendation of 100 mrem (1 mSv) applied after declaration
- Mixed feedback from stakeholders
  - In many cases, accommodation results in no additional exposure after declaration
  - Potential concern (medical) that lower value might result in decision to not declare

23

Embryo/Fetus

- Staff Recommendation:
  - Develop regulatory basis for reducing limit to 100 mrem
  - Consider options of applying over entire gestation period, or only after declaration

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ALARA Planning

- ICRP added emphasis to consistent use of optimization and use of constraints
  - Proposals to add requirements for ALARA planning to reduce highest individual exposures, instead of changing limits
  - Opposition to term constraints
  - Opposition to numeric value because it would be perceived to be a limit

ALARA Planning

- Staff Recommendation:
  - No significant change in rule text
  - Explore guidance to provide additional examples of acceptable mechanisms and programs

Units of Exposure and Dose

- Issue raised by stakeholders to move to SI units (Becquerel, Gray, Sievert)
- HPS position statement in February, 2012
- Current metrication policy states preference for SI units first, with special units in parenthetical
- Staff Recommendation:
  - Explore implications, benefits, and costs of aligning with metrication policy
  - Close interactions needed with other Federal Agencies and States

Reporting of Occupational Dose

- Seven categories required to report individual occupational doses
  - Licensees in Agreement States report as required by the State
  - Some categories of licensed use (e.g. medical) do not report
  - Database useful for assessment of impacts, inspection and enforcement, dose to an individual from multiple licensees.

Reporting of Occupational Dose

- Staff Recommendation:
  - Explore implications, benefits, and costs of requiring additional categories to report
  - Explore mechanisms to increase sharing of data between NRC and States to move towards national database

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10 CFR Part 50, Appendix I

- Methodology still based on ICRP 1 and 2
- Compliance calculations different for 10 CFR Part 20 and 10 CFR part 50
- Stakeholder encouragement to update and align dose calculation methodologies
- Staff Recommendation:
  - Initiate development of Regulatory basis for revision using updated methodology
  - Pursue rulemaking on parallel track with changes to 10 CFR Part 20

30

Backfit Considerations

- 10 CFR Part 20 applies to all licensees, including those protected by various backfitting provisions
  - Previous revision in 1991 concluded final rule provided a substantial increase in overall protection of public health and safety based on both quantitative and qualitative grounds
  - Some provisions could be considered as redefinitions of adequate protection

31

Backfit Considerations

Continued

- Other provisions would require assessment of benefits and impacts
- Both Quantitative and Qualitative arguments will be important in analysis

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Staff Recommendation

- Staff recommends approval of option to continue development of regulatory basis using recommended direction for each technical issue
- Staff recommends stakeholder outreach and participation on possible rule text, guidance, benefits, and impacts
- Staff recommends parallel regulatory basis development for proposed rules for 10 CFR Part 20 and 10 CFR Part 50, Appendix I

Questions?

Acronyms

- ALARA – As Low As Reasonably Achievable
- ALI – Annual Limit on Intake
- BEIR – Biological Effects of Ionizing Radiation
- CFR – Code of Federal Regulations
- DAC – Derived Air Concentration
- FRN – Federal Register Notice
- IAEA – International Atomic Energy Agency
- ICRP – International Commission on Radiological Protection

Acronyms

- LDE – Lens of Eye Dose Equivalent
- MPC – Maximum Permissible Concentration
- mSv – milliSieverts
- NCRP – National Council on Radiation Protection
- SECY – Office of the Secretary
- SI – International System of Units
- TEDE – Total Effective Dose Equivalent
- UNSCEAR – The United Nations Scientific Committee on the Effects of Atomic Radiation

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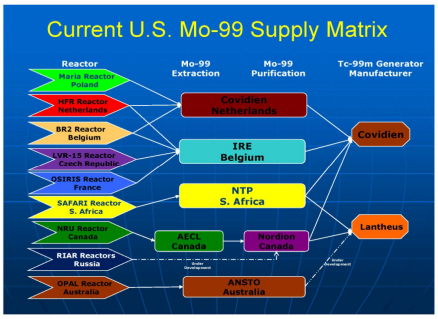
Update on the Domestic Production of Mo-99

Steve Mattmuller
Advisory Committee
on the Medical Uses of Isotopes
September 20-21, 2012

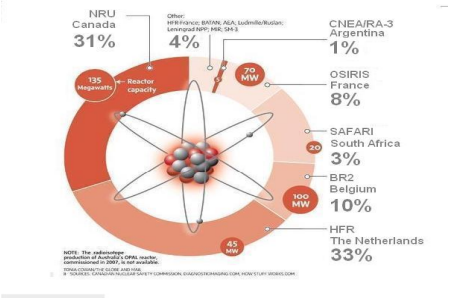
Mo99 Update: Supply – Fragile*



Covidien

2

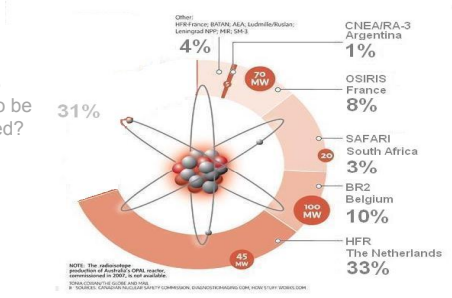
Mo99 Update: Mo99 Producers



3

Mo99 Update: Mo99 Producers

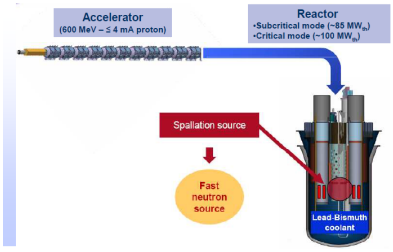
31% needs to be replaced?



4

Mo99 Update: Mo99 Producers

Replacement Reactor for the BR2 in Belgium



MYRRHA: Multi-purpose hybrid research reactor for high-tech applications

5

Mo99 Update: Mo99 Producers

Replacement Reactors: HFR in the Netherlands

PALLAS

6

Mo99 Update: Mo99 Producers

Replacement Reactors

OSIRIS

France

Jules Horowitz Reactor

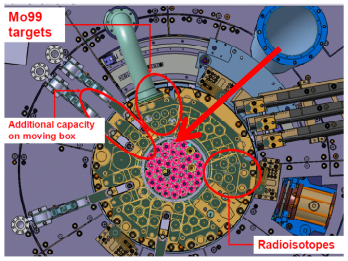
7

Mo99 Update: Mo99 Producers

Replacement Reactors

Jules Horowitz Reactor

2015



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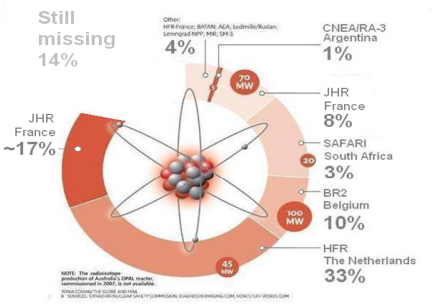
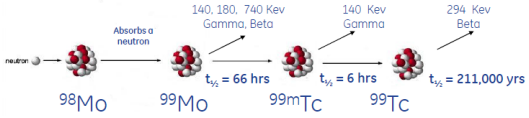
Mo99 Update: Mo99 Producers



Mo99 Update: US Domestic Mo99

Neutron Capture:

GEH process uses neutron capture to produce the parent of ^{99m}Tc from ^{98}Mo

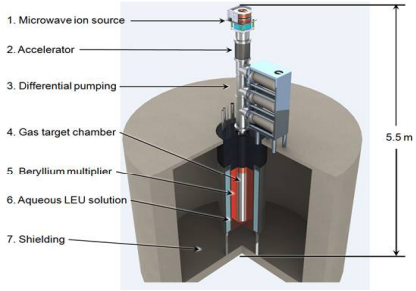


42 Protons	42 Protons	43 Protons	43 Protons
56 Neutrons	57 Neutrons	56 Neutrons	56 Neutrons
98 = Atomic Wt	99 = Atomic Wt	99 = Atomic Wt	99 = Atomic Wt

HITACHI

Mo99 Update: US Domestic Mo99

Accelerator Technology:



SHINE MORGRIDGE

Mo99 Update: US Domestic Mo99

LEU Solution Reactor Technology:

B&W MIPS Technology

Phase 1: Completed

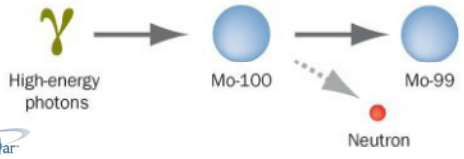
Phase 2: Addressing project business case prior to moving into next phase

B&W

Mo99 Update: US Domestic Mo99

Accelerator Technology:

High energy photons are created from a high power electron beam through bremsstrahlung.



NorthStar

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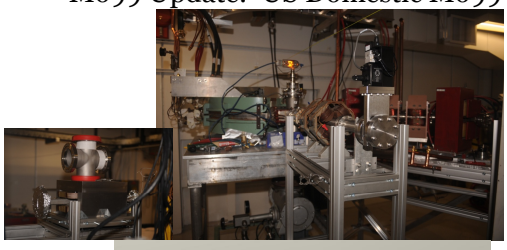
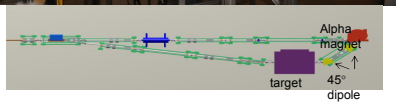
Mo99 Update: US Domestic Mo99

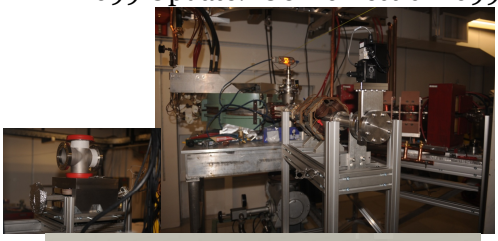




Argonne

14

Mo99 Update: US Domestic Mo99



Argonne

15

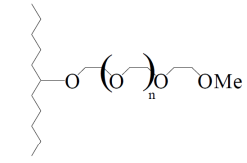
Mo99 Update: US Domestic Mo99

Argonne

16

Mo99 Update: New Tc99m Generator

ABEC - Aqueous Biphasic Extraction Chromatography

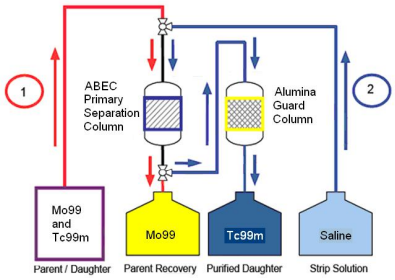


Support
Polystyrene
Divinylbenzene

n = 50

Automated two column generator systems for medical radionuclides
Daniel R. McAlister, E. Philip Horwitz; Applied Radiation and Isotopes 67 (2009) 1985-1991

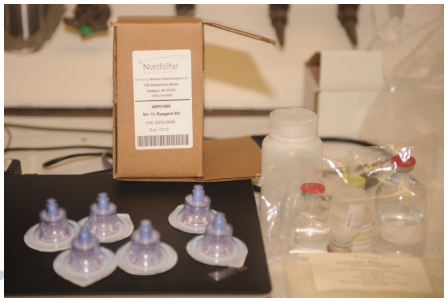
Mo99 Update: New Tc99m Generator



Mo99 Update: TechneGen™

NorthStar

Mo99 Update: TechneGen™



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Mo99 Update: TechneGen™

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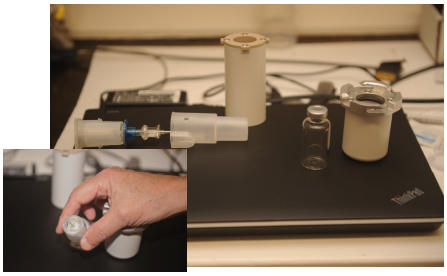
Mo99 Update: TechneGen™



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Mo99 Update: TechneGen™

23

Mo99 Update: Reimbursement

24

Acronyms

- ABEC – Aqueous Biphasic Extraction Chromotography
- AECL – Atomic Energy of Canada
- ANSTO – Australian Nuclear Science & Technology Organisation
- BR2 – Belgian Reactor 2
- CNEA – Comisión Nacional de Energía Atómica
- HFR – High Flux Reactor
- IRE – Institute for Radio-Elements
- JHR – Jules Horowitz Reactor

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Acronyms

- LEU – Low-enriched Uranium
- MIPS – Medical Isotope Production System
- Mo99 – Molybdenum-99
- NRU – National Research Universal
- NTP – Nuclear Technology Products
- RIAR – Research Institute of Atomic Reactors
- Tc99m- Technetium-99m

26

April 2013

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1 Passover	2 Passover	3 X	4 X	5 X	6
7	8 National REP Conference (CRCPD)	9 National REP Conference (CRCPD)	10 National REP Conference (CRCPD)	11 National REP Conference (CRCPD)	12 National REP Conference (CRCPD)	13 National REP Conference (CRCPD)
14	15	16	17 X	18	19	20
21	22	23	24 X	25 X	26	27
28	29	30				

May 2013

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1 X	2	3	4 ACR Annual Meeting
5 ACR Annual Meeting	6 ACR Annual Meeting	7 ACR Annual Meeting	8 ACR Annual Meeting	9	10 X	11
12	13	14	15 Shavuot	16 Shavuot	17 X	18
19 CRCPD National Conference on Radiation Control	20 CRCPD National Conference on Radiation Control	21 CRCPD National Conference on Radiation Control	22 CRCPD National Conference on Radiation Control	23 CRCPD National Conference on Radiation Control	24 X	25
26	27 Memorial Day	28	29 X	30	31 X	